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Pharmacokinetics of Sotalol Enantiomers

by

Robert Arthur Carr

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

in

Pharmaceutical Sciences (Pharmacokinetics)
Faculty of Pharmacy and Pharmaceutical Sciences

Edmonton, Alberta

Fall 1995

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Robert Carr

11708-39A Avenue
Edmonton, Alberta
CANADA
T6J 0P2

Date: May 26, 1995

March 7, 1995

As a co-author of the manuscripts: "Protein binding of sotalol enantiomers in young and elderly human and rat serum", submitted for publication in *Biopharm Drug Disp*; "Gastrointestinal and biliary clearance of sotalol enantiomers in rat model", submitted for publication in *Biopharm Drug Disp*; "Influence of cimetidine co-administration on the pharmacokinetics of sotalol enantiomers in an anesthetized rat model: evidence supporting active renal excretion of sotalol", submitted for publication to *Biopharm Drug Disp*; and "Stereospecific evaluation of sotalol pharmacokinetics in a rat model: evidence suggesting an enantiomer interaction", published in *Biopharm Drug Disp*, 1993; permission is hereby granted to include the above manuscripts, in whole or in part, in the thesis authored by Robert Carr entitled "Pharmacokinetics of sotalol enantiomers".

Signed,

Dr. Franco Pasutto

March 7, 1995

As a co-author of the manuscripts: "Protein binding of sotalol enantiomers in young and elderly human and rat serum", submitted for publication in *Biopharm Drug Disp*; and "Pharmacokinetics of sotalol enantiomers in humans", published in the *J Clin Pharmacol*, 1992; permission is hereby granted to include the above manuscripts, in whole or in part, in the thesis authored by Robert Carr entitled "Pharmacokinetics of sotalol enantiomers".

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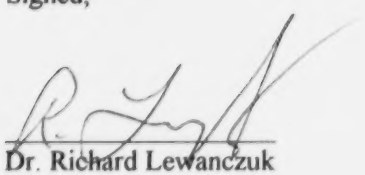

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Dr. Peter Hamilton

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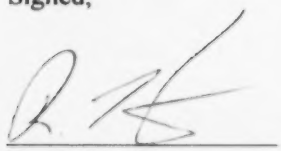

Dr. Robert Foster

University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled "Pharmacokinetics of Sotalol Enantiomers" submitted by Robert Arthur Carr in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences (Pharmacokinetics).

Co-supervisor: Dr. R.T. Foster

Co-supervisor: Dr. F.M. Pasutto

Dr. R.Z. Lewanczuk

Dr. J.A. Rogers (Chair)

Dr. Y.K. Tam

Dr. L.I. Wiebe

Dr. P. du Souich (External Reader)

Date: May 26/95

ABSTRACT

Sotalol is a unique β-adrenoceptor antagonist in that it possesses class III antiarrhythmic activity. Although racemic sotalol has been administered for over 25 years in Canada and Europe as an antihypertensive/antianginal, and for over two years in the United States as an antiarrhythmic, little is known about the disposition of the individual enantiomers. Elucidation of enantiospecific pharmacokinetics of sotalol is necessary, given: 1) stereoselective pharmacological activity (enantiomers have equipotent antiarrhythmic activity, whereas β-blocking activity is attributed to R-sotalol); 2) most β-blockers display stereoselective disposition; and 3) pure S-sotalol is being considered as an antiarrhythmic. Therefore, it was undertaken to elucidate the pharmacokinetics of sotalol enantiomers.

Disposition of sotalol in young adult volunteers after administration of the racemate was found to be non-stereoselective. Rat was then used to assess the pharmacokinetics of sotalol after administration of both the racemate and pure enantiomer. As in humans, sotalol disposition was non-stereoselective following administration of the racemate. However, when given as pure enantiomer, S-sotalol clearance was significantly reduced when compared to the racemate. This is perhaps a consequence of increased renal blood flow by the β-blocker R-sotalol. Such a pharmacodynamic enantiomer-enantiomer interaction would be unlikely in humans, where renal clearance of sotalol enantiomers is independent of renal blood flow.

Sotalol enantiomers were primarily excreted unchanged in the urine. In rat, tubular secretion was the predominant mechanism for the renal excretion of sotalol.

Tubular secretion likely accounts for one third of the total elimination of sotalol in humans. Although minor elimination pathways, sotalol was found to be excreted in the bile, and *via* intestinal clearance. Serum binding of sotalol enantiomers was negligible.

The findings of this study: 1) facilitate new interpretation of pharmacokinetic/pharmacodynamic studies where total (R- plus S-) sotalol was quantified; 2) contribute toward more complete characterization of the renal elimination of sotalol; 3) clarify uncertainty in the literature regarding the extent and stereoselectivity of serum protein binding of sotalol; 4) account for minor (non-renal) routes of elimination of sotalol enantiomers; and 5) illustrate that although a pharmacodynamic enantiomer-enantiomer interaction is likely present in rat, such an interaction may not be observed in humans.

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GLOSSARY OF ABBREVIATIONS

A	extrapolated concentration at time 0 for the distribution phase
AAG	α_1-acid glycoprotein
$Ae_{0\text{-}6h}\%$	fraction of dose excreted unchanged in the urine from 0-6 h post-dose
α	distribution phase rate constant
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
B	extrapolated concentration at time 0 for the elimination phase
β	elimination phase rate constant
C_{av}	average concentration
C_{last}	last concentration point
Cl/F	oral clearance
Cl_i	intestinal clearance
Cl_{nr}	non-renal clearance
Cl_r	renal clearance
Cl_s	systemic clearance
Cl_{sec}	net renal tubular secretion clearance
cm	centimeter(s)
CV	coefficient of variation
° C	degrees Celsius
D	dose
E	extraction ratio
f_u	free-fraction in serum
g	gram(s)
g	gravities
GFR	glomerular filtration rate

h	hour(s)
HPLC	high-performance liquid chromatography
"	inches
i.d.	inside diameter
inf.	infinity
I.S.	internal standard
IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
kg	kilogram(s)
λ_n	terminal elimination rate constant
l	liter(s)
M	male
M	molar
NEIC	S-(+)-1-(1-naphthyl)ethyl isocyanate
µg	microgram(s)
µl	microliter(s)
mg	milligram(s)
min	minute(s)
ml	milliliter(s)
MRT	mean residence time
n	number of observations
ng	nanogram(s)
nm	nanometer
o.d.	outside diameter
R	chromatographic resolution
r^2	correlation
r	$\sqrt{r^2}$
s	second(s)

SD	standard deviation
SEM	standard error of the mean
ΣXb	cumulative biliary excretion
ΣXf	cumulative excretion in the feces
ΣXu	cumulative urinary excretion
τ	dosing interval
$t_{1/2}$	half-life
U	unit(s)
U.S.A.	United States of America
UV	ultraviolet
Vd	volume of distribution
Vd_{ss}	volume of distribution at steady-state

➢ CHAPTER 1 ≺

Introduction♦

History

Sotalol is a racemic β-adrenergic blocking drug that was first discovered in 1960, before propranolol [1,2]. Racemic sotalol has been used as an antihypertensive/antianginal in Canada and Europe for more than 25 years. Sotalol is a therapeutically unique β-blocker in that β-blocking activity is combined with the ability to increase cardiac repolarization and refractoriness (class III antiarrhythmic activity). This antiarrhythmic activity of sotalol has resulted in a recent renewed interest in the drug, perhaps intensified by results from the Cardiac Arrhythmia Suppression Trial (CAST) which found an increased risk of sudden death associated with well-tolerated, effective antiarrhythmic class I agents [3]. As a result of the CAST findings, the risks *versus* benefits of antiarrhythmic therapy has come under increasing scrutiny [4]. Since 1989 the Food and Drug Administration (FDA) of the U.S.A., in response to the reported potential increased risk of mortality with antiarrhythmic therapy, has approved new antiarrhythmic drugs only for the treatment of "life-threatening ventricular arrhythmias or supraventricular arrhythmias" [4]. In 1992, racemic sotalol was approved by the FDA for use in the United States for the treatment of life-threatening ventricular arrhythmias [5].

Recent literature supports the efficacy of sotalol as an antiarrhythmic. Sotalol has been reported to be superior to other antiarrhythmic agents (including imipramine, mexiletine, pirmenol, procainamide, propafenone, and quinidine) in the treatment of sustained ventricular arrhythmias [6]. In a comparative study on the efficacy of various antiarrhythmic agents in ventricular arrhythmias, only sotalol was found to significantly reduce mortality [6]. Racemic sotalol also has demonstrated equivalent or

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superior efficacy *versus* other antiarrhythmic agents (including digoxin plus disopyramide, quinidine, and metoprolol) in the treatment of supraventricular arrhythmias [6]. The pure enantiomer S-sotalol, which has 1/50 of the β-blocking potency of its antipode, is currently undergoing clinical trials as an antiarrhythmic. The administration of the pure S-enantiomer may be advantageous when β-blockade activity is undesirable [7].

Physicochemical Properties

The chemical structure of sotalol is depicted in Figure 1-1. As the hydrochloride salt, sotalol is an odorless, white crystalline solid [8]. The molecular weights of the base and hydrochloride salt are 272.36 and 308.82, respectively. Sotalol is a relatively hydrophilic β-blocker, which is reflected by a water/*n*-octanol partition coefficient (log P value) of 0.24 [9]. Utilizing octanol/phosphate buffer (pH 7.4) at 37° C, sotalol was reported to have a partition coefficient of 0.09 [10].

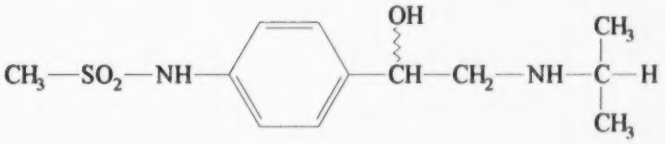

Figure 1-1. Chemical structure of racemic sotalol.

Unlike other β-blockers, which are aryloxypropanolamines, sotalol enantiomers are methanesulfonamide-substituted phenethanolamines, and thus are amphoteric. The pKa values for sotalol are 9.8 and 8.3 for the amine and the sulfonamide, respectively [11].

Optical rotations of the two pure enantiomers of sotalol hydrochloride were obtained using a Perkin Elmer model 241 polarimeter. The rotations were measured in

a 10 cm cell (water as solvent) at the sodium D-line (589 nm). The optical rotations (specific rotations) of sotalol hydrochloride were:

(+)-(S)-sotalol hydrochloride $[\alpha]_D^{26}$ + 35.80°

(-)-(R)-sotalol hydrochloride $[\alpha]_D^{26}$ - 34.75°

The specific rotations of sotalol hydrochloride in methanol were reported [12] as:

(+)-(S)-sotalol hydrochloride $[\alpha]_D^{25}$ + 39.9°

(-)-(R)-sotalol hydrochloride $[\alpha]_D^{25}$ - 36.3°

Utilizing a Uni-Melt capillary melting point apparatus (Arthur H. Thomas Company, Philadelphia, PA), the melting points of racemic sotalol hydrochloride, S- and R-sotalol hydrochloride were 218-219° C, 210-211° C, and 204-205° C, respectively. The melting point of racemic sotalol hydrochloride has previously been reported as being within the range of 206.5-207° C [11].

Mechanisms of Action

Sotalol is a competitive β-adrenoceptor antagonist devoid of intrinsic sympathomimetic and membrane-stabilizing actions. S-sotalol possesses less than 1/50 of the β-blocking activity of its antipode [7]. In animals and humans, racemic sotalol has β-blocking potency similar to that of propranolol [6].

Sotalol enantiomers have equipotent class III antiarrhythmic activity in lengthening the cardiac action potential duration (APD) and increasing the effective refractory period [6]. The lengthening of the APD appears unrelated to β-blocking activity, and is likely due to the ability of sotalol enantiomers to inhibit the time-dependent K^+ current, an increase in the magnitude of the slow inward Ca^{2+} current, or

an induction of the Na^+-Ca^{2+} exchange [2,6]. The increase in APD is associated with an increase in cardiac contractility [2]. This positive inotropic effect is not due to intrinsic sympathomimetic activity, but rather the ionic changes responsible for the increase in APD [2]. The positive inotropic and APD-lengthening effects of sotalol enantiomers are inversely related to heart rate [2].

Hemodynamic studies report that racemic sotalol reduces heart rate, cardiac index and stroke work index without changing stroke volume index or increasing left ventricular end-diastolic pressure [7].

Adverse Effects

Sotalol is generally well-tolerated: many of the observed adverse effects are dose-related extensions of its pharmacological properties [13]. Adverse effects related to β-blocking activity include fatigue, dizziness, dyspnea, headache, and worsening of bronchospasm. The incidence and nature of these adverse effects is similar to that of other β-blockers [7]. Sotalol, like atenolol, has a low incidence of central nervous system-related adverse effects due to low penetration to the brain [7]. Aggravation of congestive heart failure, a more serious complication attributed to the use of β-blockers, occurs in approximately 1.5-3% of patients with ventricular tachycardia treated with sotalol [6]. The positive inotropic activity of sotalol likely contributes to the relatively low incidence of exacerbated heart failure. Proarrhythmia is another serious adverse effect of sotalol. Torsade de pointes is an arrhythmia that is associated with prolongation of the QT interval, and is the most common form of proarrhythmia induced by sotalol. Torsade de pointes occurs in approximately 2-5% of patients with ventricular tachycardia treated with sotalol [6,13]. This is comparable to the frequency of quinidine-induced torsade de pointes. In a comparative study of several antiarrhythmic agents, sotalol was associated with the lowest rate of adverse effects [6].

Pharmacokinetics

Absorption

Although sotalol is relatively hydrophilic compared with other β-blockers [14], oral bioavailability is deemed to be 100% in humans [15] and dog [16]. Sotalol is absorbed somewhat slower than most other β-blockers, with peak concentrations of total (S- + R-) sotalol occurring within 2-4 h [7,17]. Administration of either calcium carbonate or aluminum hydroxide antacids has little effect on the absorption of sotalol [18]. Administration of sotalol with food decreases its bioavailability by approximately 18% [17].

Distribution

Sotalol is only negligibly (~0%) bound to human [15] and dog [16] plasma proteins. The volume of distribution of total sotalol is approximately 1.3 l/kg. As expected, the more lipophilic β-blockers, including metoprolol and propranolol, have greater reported volumes of distribution of 5.5 and 2.8-5.5 l/kg, respectively [14]. Interestingly, the volume of distribution appears to be somewhat reduced in elderly hypertensive subjects [19]. For example, values of 3.55 ± 0.51 and 2.22 ± 0.28 l/kg were reported for healthy young and elderly hypertensive subjects, respectively. Sotalol distributes to tissues including the liver, heart, and kidney. In rat [20] and dog [21], concentrations of total (S- + R-) sotalol in these tissues were 1.5-2.5 times greater than in plasma. As sotalol has a very low lipid solubility compared with other β-blockers, there is slow entry of drug into the brain; the brain:plasma ratio was determined as 0.52 in anesthetized cats [7].

Metabolism

Sotalol does not undergo first-pass metabolism after oral administration [7]. Following intravenous administration of ^{3}H-sotalol to dogs, over 90% of the drug was excreted renally; less than 1% of the drug was excreted in bile [22].

Excretion

Sotalol is excreted by glomerular filtration with approximately 75% of the drug being excreted within 72 h [7]. The reported elimination half-life of total sotalol ranges from 7-18 h [7]. As expected, reduced renal function (i.e., reduced creatinine clearance) results in reduced renal clearance values of total sotalol. For example, renal clearance of total sotalol has been reported [23] to be reduced from a mean of 4.99 l/h (creatinine clearance > 80 ml/min) to a mean of 0.27 l/h (creatinine clearance < 10 ml/min). In fact, after chronic administration of sotalol, the serum half-life was reported to be 69 h in an anuric patient [24].

Although in dog the renal clearance of sotalol enantiomers appears to be essentially *via* glomerular filtration [16], there is evidence that in humans active renal tubular transport may be present. Ishizaki *et al.* reported the renal clearance of total sotalol to be approximately twice that of creatinine clearance in 21 subjects ranging in age from 19-74 y [19]. This finding suggests that sotalol enantiomers undergo a net renal tubular secretion in addition to glomerular filtration, which may or may not also involve a renal tubular reabsorption component. This notion is substantiated by the data of Ishizaki *et al.* [19] in which the ratio of renal clearance of total sotalol to the glomerular filtration rate increases as the glomerular filtration rate decreases, suggesting the presence of a renal elimination mechanism that does not decline in parallel with reduced glomerular filtration.

The disposition of total sotalol after IV administration of the racemate is adequately described by a two compartment model [17]. Plasma concentrations of total sotalol were proportional to the dose (linear kinetics) when studied over the dosage range of 160-640 mg/day of the racemate [17]. After oral administration of 400 mg/day of the racemate for eight days, the pharmacokinetics of total sotalol were not significantly different from corresponding single dose values [25]. In this study, the mean ratio of the AUC (0-τ) for total sotalol at steady state to the AUC following the first dose (0-inf.) was 0.95 ± 0.18 [25].

The disposition of total sotalol appears to be comparable between obese individuals and control subjects [26]. In elderly hypertensive subjects, however, renal

clearance of total sotalol was reduced from a value of 4.10 ± 0.60 ml/min/kg which was observed in healthy young subjects, to 1.93 ± 0.32 ml/min/kg [19]. Presumably, the reduction in total sotalol renal clearance in the elderly is a reflection of the changed physiology in the elderly (e.g., reduced glomerular filtration).

Sotalol is excreted in breast milk, whereby milk:serum concentration ratios ranged from 2.43-5.64 [27]. Consequently, breast-fed infants may be exposed to relatively high sotalol concentrations.

Drug Interactions

Pharmacokinetic drug interactions involving sotalol have not been reported [17]. Co-administration of sotalol does not alter the pharmacokinetics of digoxin, warfarin, or hydrochlorothiazide [17]. It has been suggested that sotalol not be concurrently administered with calcium antagonists due to possible additive effects on atrioventricular conduction, ventricular function, or blood pressure [17]. It has also been suggested that sotalol not be concurrently administered with another drug that would prolong the QT interval, due to possible additive effects [13].

Pharmacodynamics

Attempts have been made to correlate clinical endpoints with serum sotalol concentrations. As enantiospecific sotalol concentrations were not determined in these studies, no attempt could be made to correlate clinical endpoints with the individual concentrations of the S- and R-enantiomers. Instead, the reported sotalol concentrations represent the total of both S- and R-sotalol concentrations, in an undetermined ratio.

Although it has been suggested that the therapeutic range of total (S- + R-) sotalol is 1000-3000 ng/ml, the effective concentration range for β-blockade is likely different from that for antiarrhythmic activity [13]. This notion is supported by the reported serum concentration of total sotalol required to produce a 50% reduction in maximal exercise heart rate (804 ng/ml) in patients with ectopic ventricular activity,

which is substantially less than that required to cause a significant prolongation of the QTc interval (2550 ng/ml) [13].

β-Blocking Activity

Clinically significant β-blockade occurs at plasma concentrations of total sotalol <1000 ng/ml [17]. Wang *et al.* [28] reported that the degree of β-blockade, measured as percent reduction in exercise heart rate, was well-correlated ($r = 0.79$; $p < 0.001$) to the plasma concentration of total sotalol by fitting the data from 17 patients (doses of 160-960 mg/day of racemic sotalol) to the Hill equation:

$$R = \frac{R_{max} \times C}{C_{50} + C}$$

where R = the observed percent reduction in exercise heart rate, C = the plasma concentration of total sotalol, R_{max} = the maximal reduction in heart rate expressed as a percentage (fitted), and C_{50} = the plasma concentration of total sotalol at which 50% of R_{max} occurred (fitted). The plasma concentration of total sotalol predicted to produce 50% of the maximal reduction in exercise heart rate was 804 ng/ml [28].

Unlike Wang *et al.* [28] who correlated total sotalol concentration with β-blockade utilizing a non-linear equation, Brown *et al.* [29] took a different approach, and found significant linear correlations in normal subjects (n = 5) between the percent reduction in exercise heart rate and both the logarithm of dose of racemic sotalol administered (doses of racemic sotalol ranged from 25-800 mg), as well as the logarithm of plasma concentration of total sotalol. It could be hypothesized that the difference between the Wang *et al.* [28] and Brown *et al.* [29] studies in the nature of the correlation between total sotalol plasma concentration and β-blockade may be due to differences between the studies in subjects (male and female patients with ventricular arrhythmias aged 22-72 y *versus* healthy male volunteers aged 21-39 y, respectively), sotalol dosage (160-960 mg/day dosed to steady-state *versus* 25-800 mg/day, respectively), and/or plasma concentrations of total sotalol (approximately

250-3750 ng/ml *versus* approximately 250-7500 ng/ml, respectively). However, if the Wang *et al.* [28] data are plotted as the logarithm of the plasma concentration of total sotalol *versus* β-blockade, a linear correlation similar to that of Brown *et al.* [29] is observed. Therefore, it would appear that at least over the dosage range of 25-960 mg/day the relation between plasma drug concentration and effect is amenable to correlation by either log-linear or curvilinear approaches. As pharmacological response (β-blockade) cannot indefinitely increase with increasing plasma sotalol concentration, fitting the data to an asymptotic relation such as the Hill equation (Wang *et al.* [28]) may be more appropriate.

Antiarrhythmic Activity

Significant class III antiarrhythmic activity of sotalol has been observed at concentrations of total sotalol as low as 1200 ng/ml [17], although the method used to assess changes in repolarization (e.g., the QT interval during constant-rate pacing, or the QTc interval) may substantially affect this value. A significant linear correlation was reported between the total sotalol plasma concentration and the increase in QTc interval ($n = 17$; $r = 0.642$; $p < 0.001$) following doses of the racemate ranging from 160-960 mg/day.

Antihypertensive Activity

Reduction in blood pressure does not appear to be correlated with plasma levels of total sotalol [1,19]. It must be recognized that attempts to correlate effect with total drug concentration may result in "scientific nonsense" when stereoselective disposition is present [30].

Rationale for Hypotheses

General Considerations

It is a well-recognized fact that cardiovascular disease is the most common cause of death for humans today. In fact, since the first national mortality statistics

were published in 1921, cardiovascular disease has been the leading cause of death in Canada, and has accounted for almost half of all deaths each year. The costs to society associated with cardiovascular disease are astronomical. It is known that hypertension is a contributing factor to the development of cardiovascular disease. The β-adrenoceptor antagonist drugs ("β-blockers") have long been first line therapy for the management of hypertension. Sotalol has been used in Canada and Europe for over 25 years in the management of hypertension and angina. Recent literature suggests that β-blockers may offer an advantage over class I antiarrhythmic agents in reducing sudden cardiac death of patients with ventricular tachyarrhythmia. Racemic sotalol, in particular, has received new interest in this regard, due to its unique combination of class III antiarrhythmic and β-blocking properties.

Stereochemical Considerations

All β-blockers are chiral in nature, and may assume two different conformations around each chiral center. The differing conformations are referred to as enantiomers, and may be described by their absolute configuration using the International Union of Pure and Applied Chemistry (IUPAC) system of nomenclature with prefixes R- or S-, or in reference to amino-acids using the prefixes (D)- or (L)-. Alternatively, enantiomers can be described by their rotation of plane polarized light using the prefixes (+)- or (d)- for dextrorotation, and (-)- or (l)- for levorotation.

Although most β-blockers (such as propranolol, atenolol, metoprolol, pindolol, and sotalol) have only one chiral carbon and thus two enantiomers, labetalol has two chiral carbons and thus four enantiomers. Nadolol has three chiral carbons, but has only four enantiomers, as the two chiral carbons on the aliphatic ring are fixed in the (2R, 3S) position. All β-blockers are administered as the racemate, that is equal amounts of all possible enantiomers, with the exceptions of dilevalol (a pure enantiomer of labetalol), penbutolol, and timolol, which are administered as the pure S-(-)-enantiomer.

Pharmacological Activity

Sotalol has one asymmetric center and thus exists in R- and S-enantiomer conformations. The pharmacological activities of the individual enantiomers have been documented [1,2,7]. Sotalol enantiomers have equal class III antiarrhythmic activity [1,2,7]. Although all β-blockers possess class II antiarrhythmic activity, sotalol is the only β-blocker available at this time that possesses class III antiarrhythmic activity. Amiodarone is another drug with class III antiarrhythmic activity, however, it has no β-blocking activity.

β-blocking activity almost always resides in the (-)-enantiomer, which is the S-enantiomer for most β-blockers, but the R-enantiomer in the case of sotalol. In the case of propafenone, the (+)-enantiomer is the more potent β-blocker. R-sotalol has approximately 50 times the β-blocking potency of its antipode [1,2,7].

Pharmacokinetics

In addition to the differing pharmacological profiles of β-blocker enantiomers, a wide variety of stereoselective mechanisms has been reported in the disposition of these drugs. Stereoselective gut absorption, first-pass metabolism, systemic metabolism, protein binding, renal clearance, and intestinal clearance have been observed in studies with various β-blockers. Although the extent of stereoselective disposition may be impossible to predict, a trend is observed whereby many β-blockers including propranolol [31-33], alprenolol and metoprolol [34,35], acebutolol [36], and bufuralol [37] display higher circulating concentrations of the S-enantiomer compared with its antipode.

Another trend can be observed in the pharmacokinetics of β-blockers in that lipophilic β-blockers such as propranolol and metoprolol are eliminated predominantly *via* hepatic metabolism, β-blockers with intermediate lipophilicity such as pindolol are eliminated both renally and nonrenally, and β-blockers that are hydrophilic, such as atenolol and sotalol are eliminated predominantly *via* the kidney. Although sotalol enantiomers may be predominantly eliminated as intact drug in the urine, this does not

preclude stereoselective disposition. In fact, the pharmacokinetics of atenolol (the β-blocker that has perhaps the most physicochemical similarity to sotalol) in humans has been reported to include stereoselective bioavailability perhaps as a result of stereoselective absorption from the gastrointestinal tract (R > S; [38]), and stereoselective renal clearance (S > R; [39]).

Although sotalol has been marketed and administered as the racemate for over 25 years, almost no information exists regarding the enantiospecific pharmacokinetics in humans or in animal model. Given the propensity of β-blockers in general, and atenolol in particular, to exhibit stereoselective disposition after administration of the racemate, it was hypothesized that the disposition of sotalol following administration of the racemate would also involve stereoselective process(es) (Hypothesis 1).

In addition to delineating the pharmacokinetics of sotalol following administration of the racemate, it was also of interest to consider the possible pharmacokinetic consequences of administration as pure enantiomer since S-sotalol is being investigated for use as an antiarrhythmic. The disposition of S-sotalol may be different when given alone compared with administration as the racemate if an enantiomer-enantiomer interaction is present. For example, a pharmacodynamic interaction between enantiomers may exist if the pharmacologic effect associated with one enantiomer influences the physiological process(es) by which the other enantiomer is handled. An interaction of this nature has been shown for propranolol where S-propranolol decreased the clearance of both enantiomers by decreasing hepatic blood flow [40]. The likely mechanism of this enantiomer-enantiomer interaction is that when S-propranolol (the enantiomer possessing the β-blocking activity) is administered either alone or as the racemate, cardiac output is reduced which results in reduced hepatic blood flow and thus reduced clearance of propranolol enantiomer(s). When R-propranolol is administered alone, hepatic blood flow is unchanged and the clearance of R-propranolol is greater than when the S-enantiomer is present.

It was hypothesized (Hypothesis 2) that a pharmacodynamic interaction could be present with sotalol enantiomers, due to the differing pharmacological activities of the enantiomers. As sotalol enantiomers are primarily cleared by the kidney, it was

hypothesized that when R-sotalol (the enantiomer possessing the β-blocking activity) was administered either alone or as the racemate renal blood flow would be different than when S-sotalol was given alone. As the effect of β-blockers on renal blood flow is variable, it is impossible to predict whether R-sotalol would increase, decrease, or not affect renal blood flow. The extent to which the hypothesized effect of R-sotalol on renal blood flow affected the renal clearance of sotalol enantiomers would depend in part on the nature of the renal elimination of sotalol. For example, if the renal clearance of both sotalol enantiomers was small compared with renal blood flow, changes in renal blood flow would be unlikely to affect renal clearance. Based on reports of the renal clearance of sotalol in healthy humans ranging from 100 ml/min [41] to approximately 250 ml/min [19] and assuming a renal blood flow of 1 l/h, the extraction ratio of sotalol by the kidney would be approximately 0.15. As a low extraction drug in humans, the renal clearance of sotalol would be relatively unaffected by perturbations in renal blood flow. Nevertheless, such alterations in renal (and/or hepatic) blood flow would have the potential to affect the disposition of concurrently administered high-extraction drugs.

In addition to interest in the effect of administration of individual sotalol enantiomers on renal clearance, the processes involved in the renal elimination were also of interest. Reports of sotalol disposition in humans suggested that active tubular secretion contributed to sotalol elimination, as renal clearance exceeded the estimated glomerular filtration rate [15,19,41]. Elucidation of an active renal tubular transport mechanism for sotalol enantiomers would not only be useful in furthering understanding of sotalol enantiomer disposition, but may also be useful in predicting and understanding drug-drug interactions with sotalol. Net active renal tubular secretion of another β-blocker, pindolol, has been reported to be likely since renal clearance values for pindolol enantiomers were approximately double that of the estimated glomerular filtration rate [42]. It was hypothesized by the authors that stereoselective renal tubular secretion was responsible for the observed significant stereoselectivity in the renal clearance of pindolol [42]. It was therefore hypothesized

that the renal clearance of sotalol enantiomers may include net active renal tubular secretion (Hypothesis 3).

Net renal tubular secretion clearance (Cl_{sec}) can be calculated as $Cl_{sec} = Cl_r - GFR \cdot f_u$, where Cl_r is the renal clearance, GFR is the glomerular filtration rate, and f_u is the unbound fraction. It is noted that Cl_{sec} is the *net* tubular clearance, and may be include both tubular secretion and tubular reabsorption mechanisms. The accuracy of the estimation of Cl_{sec} is dependent on the accuracy of the estimations of Cl_r, GFR, and f_u. The value of Cl_r for each sotalol enantiomer can be determined by standard pharmacokinetic principles. The value for GFR can be accurately estimated from a serum creatinine concentration. The value for f_u for each sotalol enantiomer can either be experimentally determined or estimated from literature values. Estimation of f_u from literature values led to uncertainty, as non-stereospecific reports in humans [15] and dog [16] found negligible serum binding of sotalol, whereas a more recent report found plasma protein binding of 38 and 35% for S- and R-sotalol, respectively [43]. Recognizing that the estimation of Cl_{sec} for sotalol enantiomers would be substantially different using values of either 1.0 or approximately 0.6 for f_u, it was deemed necessary to experimentally determine the serum protein binding of sotalol enantiomers. Given the albeit weak preponderance of evidence, it was hypothesized that sotalol was negligibly bound to serum proteins (Hypothesis 4).

Although sotalol enantiomers are primarily eliminated as intact drug in the urine, the disposition of a significant fraction (15-30%) of an oral [19,41,43] or intravenous dose [41] remains unaccounted for. Sotalol enantiomers are very nearly completely bioavailable following oral administration [41] and no known sotalol metabolites have been reported. Elucidation of the nature of the nonrenal elimination pathway for sotalol enantiomers would be useful in further understanding the disposition of sotalol and in predicting drug-drug and/or disease/drug interactions. Furthermore, as renal function and consequently renal clearance of sotalol enantiomers decrease with age, nonrenal clearance may assume increasing importance in the overall elimination of sotalol enantiomers with age and/or renal dysfunction. Sotalol enantiomers are relatively polar and have molecular weight that approaches 300 and as

such would be suitable candidates for biliary secretion. It was hypothesized that sotalol may be eliminated as intact drug in the bile (Hypothesis 5). It was also hypothesized that sotalol enantiomers may be eliminated as intact drug in the feces *via* intestinal clearance (Hypothesis 6), as intestinal clearance has been reported for other β-blockers including celiprolol [44], propranolol [44], pafenolol [45], and acebutolol [46]. As the majority of an administered dose of sotalol is recovered as intact drug in the urine, potential routes of elimination including biliary and intestinal clearance would not likely play an important role in sotalol disposition in healthy subjects. However, in renal disease non-renal routes of elimination may assume increased importance: sotalol is frequently administered to elderly patients with compromised renal function. In fact, non-renal clearance of sotalol in elderly hypertensive patients (63.6±1.3 y) constituted 43% of the oral clearance [19]. In this light, elucidation of non-renal clearance mechanisms for sotalol assumes increased importance.

Finally, it was proposed that nonrenal clearance could be completely accounted for by biliary and/or intestinal clearances of intact sotalol enantiomers, thus supporting the hypothesis that sotalol enantiomers are not metabolized (Hypothesis 7).

Hypotheses

1. The disposition of sotalol is stereoselective after administration of the racemate.
2. There exists an enantiomer-enantiomer interaction in the disposition of sotalol.
3. Renal excretion of sotalol enantiomers includes active renal tubular secretion.
4. The serum binding of sotalol is negligible and non-stereoselective.
5. Sotalol enantiomers are excreted as intact drug in the bile.
6. Sotalol enantiomers are eliminated as intact drug in the feces *via* intestinal clearance.
7. Sotalol enantiomers are not metabolized.

Objectives

1. Develop a sensitive and convenient HPLC assay capable of accurately and precisely measuring sotalol enantiomers in biological samples.
2. Delineate the pharmacokinetics of sotalol enantiomers in healthy volunteers following oral administration of the racemate.
3. Delineate the pharmacokinetics of sotalol enantiomers after administration of the racemate and pure enantiomers in rat.
4. Delineate the pharmacokinetics of sotalol enantiomers in rat in the presence and absence of cimetidine.
5. Delineate the magnitude of serum protein binding of sotalol enantiomers in young and elderly adult humans and rat.
6. Delineate the extent of biliary and intestinal clearance of sotalol enantiomers in rat.

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➢ CHAPTER 2 ≺

Stereospecific High-Performance Liquid Chromatographic Assay of Sotalol in Plasma♦

Introduction

Despite the fact that the enantiomers of sotalol (Figure 2-1) have differing activities [1-5], reported methods for analyzing sotalol in biological samples have, to date, utilized non-stereospecific techniques [6-13]. Thus, these non-stereospecific assays cannot be used to delineate the pharmacokinetics and pharmacodynamics of the enantiomers after administration of the racemate. In this report, we describe a convenient and sensitive HPLC method for the determination of sotalol enantiomers in human plasma.

Materials and Methods

Chemicals

The pure enantiomers of S- and R-sotalol, as well as racemic sotalol were obtained as gifts from Bristol-Myers (Ottawa, Ontario, Canada). Racemic atenolol hydrochloride was used as the internal standard (I.S.), and was obtained from ICI Pharma (Mississauga, Ontario, Canada). The enantiopure derivatizing reagent, S-(+)-1-(1-naphthyl)ethyl isocyanate (NEIC, Figure 2-1), was obtained from Aldrich (Milwaukee, WI, U.S.A.). Analytical grade sodium hydroxide, methanol, glacial acetic acid and chloroform were obtained from BDH chemicals (Toronto, Ontario, Canada) while analytical grade ethyl acetate and hexane, and HPLC grade water were obtained from Mallinckrodt (Paris, KT, U.S.A). Analytical grade triethylamine was obtained from Fisher Scientific (Fair Lawn, NJ, U.S.A.).

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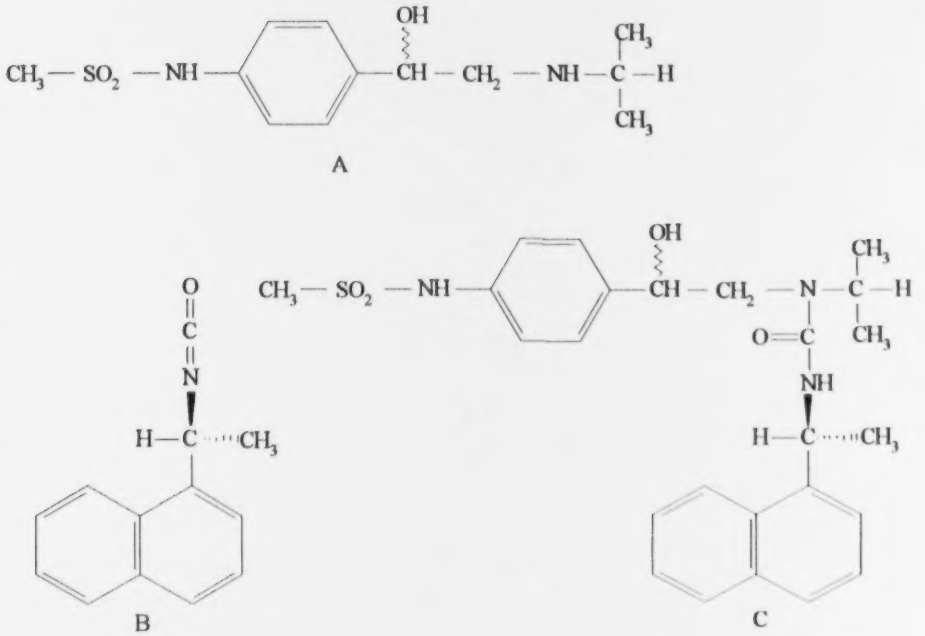

Figure 2-1. Chemical structures of (A) racemic sotalol; (B) (S)-(+)-NEIC; and (C) derivatized sotalol.

Apparatus and Chromatography

Both reversed-phase and normal-phase conditions were used for determination of enantiomer concentration and derivatization, respectively. In both cases, the HPLC system consisted of a model 590 pump, model 712 Wisp autosampler, model 745B integrator (Waters, Mississauga, Ontario, Canada).

The normal-phase chromatography utilized a 25 cm stainless steel silica column (Whatman Partisil 5, Clifton, NJ, U.S.A.). Fluorescence detection (Applied Biosystems model 980, Technical Marketing Associates, Edmonton, Alberta, Canada) was set at 220 nm for excitation; no emission filter was used. The mobile phase was chloroform:hexane:methanol (65:33:2 v/v) pumped at a flow rate of 2.0 ml/min.

The reversed-phase consisted of a Nova-Pak C_{18} 8 mm cartridge which was housed in an 8 mm X 10 cm radial compression module (Waters, Mississauga, Ontario, Canada). Fluorescence detection excitation was set at 235 nm; no emission

filter was used. The mobile phase was water:methanol:acetic acid (64:35:1) pumped at 2 ml/min.

All samples were vortexed using a Vortex Genie 2 mixer (Fisher Scientific, Edmonton, Alberta, Canada) and centrifuged with a Dynac II centrifuge (Becton Dickinson, Parsippany, NJ, U.S.A.). Solvents were evaporated using a Savant Speed Vac concentrator-evaporator (Emerston Instruments, Scarborough, Ontario, Canada).

Standard Solutions

A 100 μg/ml stock solution of racemic sotalol hydrochloride (as the base) was prepared in HPLC grade water (solution 1). The I.S. solution consisted of 10 μg/ml (as the base) of racemic I.S. in HPLC grade water (solution 2). Another stock solution of sotalol (used to determine extraction and derivatization yields) was prepared as 0.00375% triethylamine in methanol (v/v) to give a final concentration of 100 μg/ml of the base (solution 3). These solutions were stored at 5° C. The NEIC solution was prepared in chloroform (0.05% v/v) and was stored at -20° C until just prior to use.

Sample Preparation

Drug-free human plasma samples (0.5 ml each) were spiked with sotalol (solution 1) to give final concentrations of 50, 100, 250, 500, 1000, 2500, and 5000 ng/ml of each enantiomer. To this was added 5 μg of each enantiomer of I.S. (solution 2) and 30 μl of 1 *M* sodium hydroxide. The plasma was vortexed for 30 s and centrifuged at 1800 *g* (5 min) with two consecutive 4 ml volumes of ethyl acetate. The two ethyl acetate extracts obtained from each sample were combined and evaporated to dryness using the Savant Speed Vac concentrator-evaporator. Samples were then derivatized at room temperature with 0.2 ml of the NEIC solution which was added to the residue. After addition of NEIC, tubes were vortexed for 30 s and aliquots ranging from 75 to 150 μl were injected into the HPLC.

Extraction Yield

Solutions of either 100, 500 or 2500 ng/ml sotalol enantiomers (solution 3, n = 3) were added to clean, dry glass tubes and evaporated to dryness. After addition of 0.5 ml plasma to each tube, samples were extracted after addition of 30 µl 1 *M* sodium hydroxide and ethyl acetate (2 volumes of 4 ml each). The tubes were then vortexed for 30 s and centrifuged (1800 *g*, 5 min) and the two extracts of each sample were combined in clean tubes, evaporated to dryness, derivatized and chromatographed. To compare these samples with those that were not extracted, another set of tubes containing the above concentrations was prepared without the addition of plasma and subsequent extraction procedure. Peak areas of extracted sotalol *versus* unextracted equivalent Sotalol concentrations were compared under identical chromatographic conditions.

Derivatization Yield

Using solution 3, concentrations of either 250 or 1000 ng of sotalol enantiomer (n = 6 for each concentration) were evaporated to dryness. To three samples of each concentration was added 0.2 ml of NEIC solution. These derivatized samples were compared to another 3 samples that were not derivatized after injection of aliquots ranging from 25 to 50 µl into the HPLC.

Applicability to Pharmacokinetic Studies

To test the utility of the stereospecific assay for pharmacokinetic studies, a single 160 mg racemic dose of sotalol was administered orally to a healthy 25 y old male subject giving informed consent. Blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h *via* an indwelling catheter inserted in a forearm vein. Plasma was collected by centrifugation and samples were stored at -20° C until the next day for analysis.

Treatment of Data

The peak area ratio of sotalol/I.S. was used to determine the concentration of each enantiomer. The first eluting I.S. peak was used in these ratio calculations. Results are reported as mean ± SD.

Results and Discussion

Separation, identification and quantification of racemic compounds has received widespread attention [14,15]. To date, separation of drug enantiomers has been accomplished using either chiral stationary phases [16] or enantiopure reagents [17]. Recently, our laboratory reported the stereospecific analysis of acebutolol and its metabolite diacetolol, as well as tocainide using (S)-(+)-NEIC as the derivatizing reagent [19-21]. This analytical technique has since been applied to study the pharmacokinetics of acebutolol and diacetolol in healthy subjects [22].

In this report, separation of sotalol enantiomers was achieved using the enantiopure reagent (S)-(+)-NEIC, thus forming diastereomers (Figure 2-1) which were chromatographed by normal-phase HPLC. Using this method, individual enantiomers of sotalol were measured in human plasma. To our knowledge, this is the first assay reported for the analysis of sotalol enantiomers in plasma.

The reaction of NEIC with sotalol enantiomers resulted in baseline resolution of both sotalol and I.S. diastereomers ($R > 1.5$, Figure 2-2). Formation of these diastereomers seemed to occur virtually immediately, as incubation of samples using various concentrations of NEIC, at various times and temperatures did not enhance derivatization. Peaks corresponding to the sotalol enantiomers eluted at approximately 7.5 and 8.7 min. The first and second eluting sotalol peaks corresponded to S- and R-sotalol, respectively, as confirmed by chromatography of the pure enantiomers. The R- and S-I.S. eluted at approximately 20 and 23 min, respectively. Consequently, the total run time for the assay was 25 min which allowed for convenient processing of numerous clinical samples.

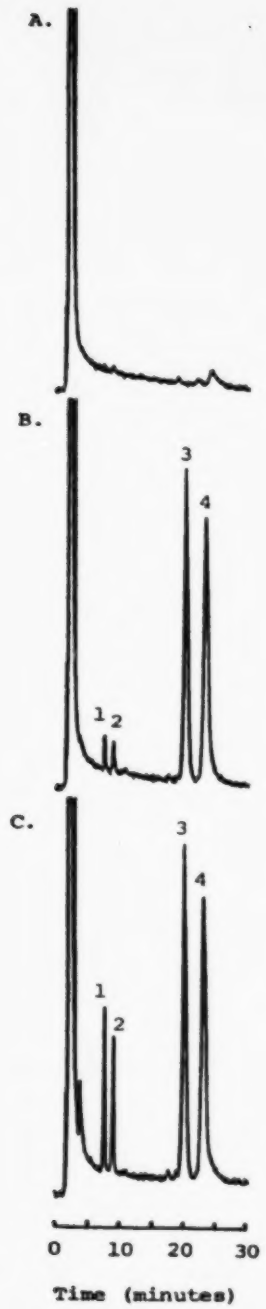

Figure 2-2. HPLC chromatograms of (A) blank plasma; (B) plasma spiked with 50 ng/ml of each sotalol enantiomer, and (C) plasma sample taken 12 h after a single oral 160-mg dose of racemic sotalol. Peak identification: 1 = S-sotalol; 2 = R-sotalol; 3 = R-I.S.; 4 = S-I.S.

The assay was accurate, precise and reproducible as summarized in Table 2-1. Chromatograms were free from interfering peaks, and calibration curves for S- and R-sotalol were typically described by y = -0.0141 + 0.000910(x), and y = -0.0126 + 0.000910(x), respectively. These equations were described where y is the peak area ratio and x is enantiomer concentration (x and y were not weighted). Excellent linearity was observed for all calibration curves ($r^2 > 0.999$), and accuracy (%error) and precision (%CV) exceeded 10% only for the lowest concentration studied. Although the reported sensitivity of this assay was 50 ng/ml, greater sensitivity in the order of 20 ng/ml was obtained using a signal:noise ratio of 4:1.

Table 2-1. Accuracy and precision of the method.

Enantiomer concentration (ng/ml)[a]						
	Measured[b]		*Accuracy, error %*		*Precision, CV %*	
Added	*S*	*R*	*S*	*R*	*S*	*R*
50	49.0±5.9	49.2±6.2	11.3	11.8	12.0	12.6
100	99.5±5.2	99.9±5.5	5.5	4.9	5.3	5.5
250	245±5.1	244±4.9	2.3	2.2	2.1	2.0
500	495±13	495±13	2.2	2.1	2.6	2.6
1000	970±43	971±44	4.0	4.2	4.5	3.4
2500	2510±85	2510±84	2.7	2.7	3.4	3.4
5000	5030±111	5030±111	1.8	1.7	2.2	2.2

[a] $n = 9$ (3 sets for 3 days).
[b] Reported as mean ± SD.

Derivatization of structurally similar compounds with NEIC has been reported to be virtually complete [18]. When using isocyanates to derivatize β-blocking drugs, previous studies have confirmed the formation of a urea, and not a carbamate, derivative [18,19]. Furthermore, the reaction between the β-blocker and the isocyanate was on a 1:1 molar basis [19]. To determine the efficiency of the derivatization with sotalol, we tried to detect underivatized drug under either the stated normal-phase conditions or with changes to the mobile phase composition. Despite our efforts, however, underivatized sotalol was not detected. Consequently, a modification of a previously reported non-stereospecific reverse-phase HPLC method was utilized [10] to detect underivatized sotalol. Using this method, underivatized

samples containing either 250 or 1000 ng of each sotalol enantiomer resulted in a single peak at 3.38 min which corresponded to racemic sotalol. Once samples were derivatized, the 3.38 min peak was absent, even at sotalol enantiomer concentrations of up to 1000 ng/ml. This data suggests that derivatization of sotalol under the stated conditions was complete (> 99%). Asymmetric induction was not observed during the derivatization of sotalol enantiomers, as the peak areas corresponding to the diastereomers were consistently equal. Finally, the diastereomers of both sotalol and I.S. appeared to be stable for at least 24 h, as changes were not observed with the chromatograms upon repeated injection of the same samples at ambient temperature.

The extraction yield of sotalol from plasma was ~ 75% over the concentration range studied. Although the extraction was not 100% it was, nevertheless, sufficient to allow for the requisite sensitivity after administration of commonly used sotalol doses.

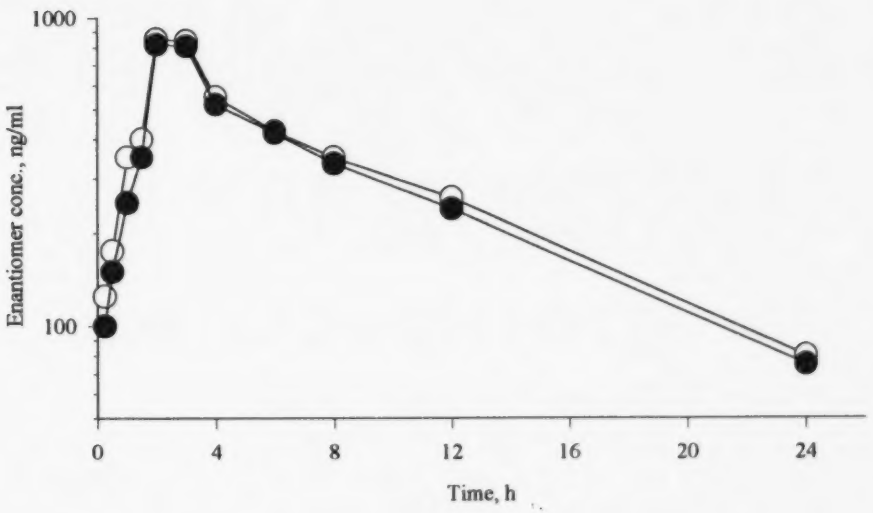

Figure 2-3. Plasma concentration versus time profiles of S-sotalol (open circles) and R-sotalol (filled circles) in a healthy 25 y old male volunteer following a single oral 160 mg dose of racemic sotalol.

The plasma concentration *versus* time profile of S- and R-sotalol after oral administration of 160 mg racemic sotalol to a healthy 25 y old male volunteer is depicted in Figure 2-3. Although concentrations of S-sotalol were generally greater than those of R-sotalol, little stereoselectivity was observed.

In conclusion, the described assay is sensitive and convenient, allowing for numerous samples to be processed in a relatively short span of time. Furthermore, the assay is applicable to pharmacokinetic studies of sotalol in humans.

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➢ CHAPTER 3 ≺

Pharmacokinetics of Sotalol Enantiomers in Young Adults♦

Introduction

Despite the fact that the enantiomers of sotalol have differing pharmacologic properties [1-8], and that pure S-sotalol is being considered for use as an antiarrhythmic agent [9-10], the pharmacokinetics and pharmacodynamics of the enantiomers after administration of the racemate have, to date, not been determined. Utilizing a stereospecific high-performance liquid chromatographic (HPLC) assay [11], we report the pharmacokinetics of sotalol in healthy human subjects.

Materials and Methods

Drug Administration and Sample Collection

A total of 8 healthy volunteers (Table 3-1) participated in the study after giving written informed consent. Volunteers were included in the study only if they: were 18 y of age or older; were male; had no known kidney dysfunction; and had not taken any β-adrenergic receptor antagonist in the month prior to the study. The protocol was approved prior to the study by the Human Ethics Review Committee of the University of Alberta Hospital, Edmonton, Canada.

On the day of the experiment, a single, oral 160 mg tablet of racemic sotalol (Sotacor, Bristol-Myers Squibb) was administered (at 0800 h) following an overnight fast beginning at 2400 h the day prior to the study. Venous blood (8 ml) was drawn into heparinized tubes at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, and 24 h *via* an indwelling catheter inserted into a forearm vein. After collection of blood, samples

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Carr RA, Foster RT, Lewanczuk RZ, Hamilton PG. *J Clin Pharmacol* 1992;32:1105-1109.

were immediately centrifuged and the plasma was separated. Serum was collected just prior to drug administration for creatinine determination. Urine (total output) was collected at time 0 and then at intervals of 0-3, 3-6, 6-12, and 12-24 h and aliquots were saved. Both plasma and urine samples were stored at -20° C until needed for analysis.

Table 3-1. Patient characteristics.

Patient	*Age, y*	*Sex*	*Weight, kg*	*Creatinine Clearance, ml/min*
1	33	M	72.0	89.2
2	26	M	80.8	115.2
3	34	M	87.9	98.5
4	37	M	89.9	98.9
5	35	M	65.3	94.8
6	28	M	78.2	110.3
7	33	M	90.7	133.8
8	31	M	68.5	102.9
Mean:	32		78.7	105.4
SD:	3		9.2	13.2

Stereospecific HPLC Analysis of Sotalol

Enantiomers of sotalol were measured utilizing a previously developed HPLC assay [11]. Following addition of racemic atenolol (internal standard, I.S.), enantiomers of sotalol were extracted from either alkalinized plasma or urine into ethyl acetate. The organic layer was evaporated and the remaining residue was derivatized with 0.05% (v/v) S-(+)-1-(1-naphthyl)ethyl isocyanate (NEIC) in chloroform. The diastereomers corresponding to derivatized sotalol and I.S. were chromatographed using normal-phase HPLC with fluorescence detection set at 225 nm for excitation, with no emission filter.

Serum Creatinine

Serum samples were analyzed for creatinine using a MicroCentrifugal Analyzer, Multistat III (Instrumentation Laboratory, Spokane, WA, U.S.A.). Creatinine clearance was estimated by the method of Cockroft and Gault [12].

Pharmacokinetic Data Analysis

For each subject, the terminal half-life of elimination ($t_{1/2}$) of the enantiomers was determined by $0.693/\lambda_n$, where λ_n (elimination rate constant) was calculated using the regression slope of the terminal elimination phase. The area under the plasma concentration *versus* time curve from time zero to infinity (AUC), the corresponding area under the first moment curve (AUMC) and mean residence time (MRT) for each enantiomer were determined for each subject using a Lagran computer software program [13]. Oral clearance (Cl/F) was calculated by dividing the total administered enantiomeric dose with the AUC. Apparent volume of distribution (Vd_β/F) was calculated by dividing Cl/F by λ_n. The fraction of the dose reaching the systemic circulation (F) could not be accurately calculated as only oral doses were administered.

The renal clearance (Cl_r) of each enantiomer was estimated by dividing the 24 h cumulative urinary excretion of each sotalol enantiomer by the corresponding 24 h AUC.

Statistical Analysis

The pharmacokinetic parameters of sotalol enantiomers were compared using a Student's *t* test for paired data. All tests were conducted at $\alpha = 0.05$. Data are expressed as mean ± SD.

Results

The mean plasma concentration *versus* time profile of sotalol enantiomers is presented in Figure 3-1. Table 3-2 summarizes the pharmacokinetic parameters of S- and R-sotalol. In this sample of subjects, the time-course of the two sotalol

enantiomers in plasma was virtually superimposable (i.e., not stereoselective). Maximal concentrations of both enantiomers were attained within about 3 h and declined with a $t_{1/2}$ of approximately 8 h. The respective MRT for S- and R-sotalol were 13.2 ± 1.2 and 12.9 ± 1.8 h. Oral clearance was, on average, 11.7 ± 1.4 and 12.4 ± 3.1 l/h for S- and R-sotalol, respectively. As expected, the majority (approximately 75%) of the oral clearance was attributed to renal clearance. Urinary excretion was not stereoselective.

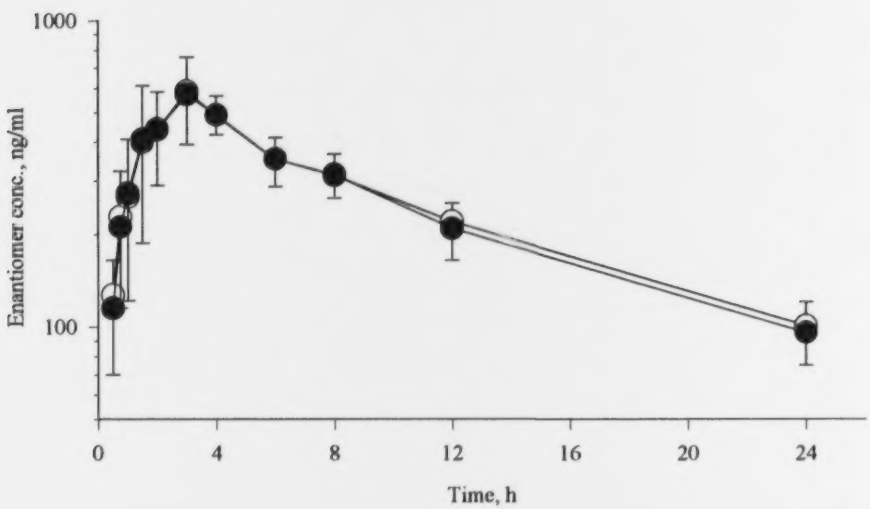

Figure 3-1. Average plasma concentration versus time profile for S- and R-sotalol (n = 8). S-sotalol = open circles; R-sotalol = filled circles; error bars represent SD.

There was little subject-to-subject variability between the pharmacokinetic parameters of the enantiomers partly due, perhaps, to the relatively high reported values of F which have been reported to approximate 100% [1,14-18], and the absence of significant first-pass metabolism [14,15,18,19].

Table 3-2. Pharmacokinetic parameters.

	$AUC_{0\text{-}inf}$, (mg/l)*h		$t_{1/2}$, h		Cl/F, l/h		Clr, l/h		MRT, h		Vd_β/F, l/kg	
Subject	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*
1	5.85	6.35	8.96	9.42	13.7	12.6	8.99	8.21	14.2	14.80	2.46	2.38
2	5.81	3.97	7.71	5.44	13.8	20.2	11.7	15.0	12.6	9.72	1.90	1.96
3	8.10	7.45	7.44	6.57	9.88	10.7	8.17	9.29	12.6	11.4	1.21	1.31
4	6.98	7.12	8.01	8.67	11.5	11.2	9.43	8.89	13.3	14.2	1.48	1.56
5	7.35	7.71	7.15	7.26	10.9	10.4	7.68	7.85	10.6	10.9	1.74	1.68
6	7.03	7.28	7.91	8.55	11.4	11.0	6.79	7.01	13.1	13.9	1.67	1.75
7	6.34	6.33	8.96	8.40	12.6	12.6	10.4	10.2	14.7	14.0	1.79	1.70
8	8.11	7.86	9.04	8.60	9.86	10.2	8.65	9.29	14.4	13.9	1.86	1.83
Mean:	6.95	6.76	8.15	7.86	11.7	12.4	8.98	9.46	13.2	12.9	1.76	1.77
SD:	0.9	1.2	0.7	1.2	1.4	3.1	1.5	2.3	1.2	1.8	0.36	0.31

Discussion

To our knowledge, this is the first report of sotalol enantiomer disposition utilizing stereospecific methods in humans after administration of the racemate. There was, however, a previous report by Poirier *et al.* [15] where the disposition of S-sotalol in human plasma was compared to the disposition of racemic sotalol. The assay for sotalol in their report, however, utilized a non-stereospecific method. Poirier *et al.* [15] concluded that there were no significant differences in pharmacokinetic parameters obtained following S-sotalol administration compared with racemate. Nevertheless, as pointed out by others [20-22], valid conclusions regarding disposition of chiral compounds can only be made by examining the disposition of the individual enantiomers. The possibility that the time course of a single enantiomer after administration as such may be different as compared to when the isomer is administered as the racemate should be considered. Such a difference, for example, could arise as a consequence of an enantiomer-enantiomer interaction. In fact, preliminary studies describing the pharmacokinetics of sotalol enantiomers in a rat model after administration of either racemic sotalol or pure enantiomer suggested the possible existence of such an enantiomer-enantiomer interaction [23]. An enantiomer-enantiomer interaction has been previously demonstrated in the case of propranolol [24].

Sotalol is virtually completely absorbed after oral dosing [1,14,17,18], does not undergo first-pass metabolism [14,15,18,19], is only negligibly bound to plasma proteins [18], and is mainly excreted intact in urine [1,14,16-18,25]. As expected, therefore, it is unlikely that sotalol would exhibit stereoselective pharmacokinetics apart from, perhaps, stereoselective renal clearance. Stereoselective renal clearance has previously been reported for another relatively hydrophilic β-blocking drug, atenolol [26]. As Cl_r values in the present study were, on average, 1.5-fold greater than creatinine clearance values, it is likely that active tubular secretion of sotalol enantiomers exists.

The observed oral clearance values for S- and R-sotalol were 11.7 ± 1.4 and 12.4 ± 3.1 l/h, respectively. These values were greater than the Cl_r of 8.98 ± 1.5 and 9.46 ± 2.3 l/h, respectively, for S- and R-sotalol. Assuming that the sotalol dose was completely absorbed [1,14,17,18], nonrenal clearance may constitute up to approximately 23% of oral clearance. It is noted that support for the assumption of complete bioavailability is at present weak. Indeed, as yet there is no published report of the range or variability of oral bioavailability of sotalol in a sample of subjects. Although there remains little evidence for metabolism of sotalol in man [17-19], other pathways of clearance such as biliary secretion may be present. Furthermore, direct secretion of drug across gut wall may occur, as has been reported for acebutolol in both rat [27,28] and dog [27-29].

The pharmacokinetic parameters of sotalol enantiomers obtained in this study agree with those previously reported by others using non-stereospecific methods [15,17,18,30]. These values did, however, differ from that reported in one study by Ishizaki *et al.* [16], who reported mean Cl_s values in healthy volunteers of 5.93 ± 1.00 ml/min/kg and Cl_r values approximately twice that of creatinine clearance. In healthy volunteers, Cl_r accounted for 70% of oral clearance. In elderly hypertensive patients, the magnitude of renal clearance of sotalol was 1.9 ml/min/kg, which was less than one half the corresponding value for healthy volunteers, but still substantially exceeded the measured creatinine clearance [16]. Interestingly, 70% of the subjects conducted by Ishizaki *et al.* [16] undertook a vigorous exercise test during the study. Consequently,

the altered physiology as a function of exercise on the pharmacokinetic indices needs to be more carefully scrutinized. Also, in elderly hypertensive patients Cl_r accounted for only 58% of oral clearance, thus supporting the notion of a clearance mechanism(s) that does not decline in parallel with glomerular filtration.

In conclusion, the plasma disposition of sotalol enantiomers after administration of racemate to healthy subjects was not stereoselective. Despite the likelihood of active renal tubular secretion of sotalol enantiomers, stereoselective renal clearance was absent. Regardless of these findings, caution must be exercised when attempting to apply these results to various patient populations. Furthermore, the pharmacokinetics obtained in this study after racemate administration should not be extrapolated to that after administration of a pure isomer even though the time course of enantiomers was not different.

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➢ CHAPTER 4 ≺

Pharmacokinetics of Sotalol Enantiomers in Rat Model: Evidence Suggesting an Enantiomer-Enantiomer Interaction♦

Introduction

Although the enantiomers of sotalol have differing pharmacologic activities [1-14], data describing the stereospecific pharmacokinetics of sotalol is sparse. In a study by Poirier *et al.* [15], the authors reported that there was no significant difference in the disposition of S-sotalol in humans when administered as the pure enantiomer compared with the same enantiomer administered as the racemate. However, this study analyzed sotalol utilizing a non-stereospecific method and was therefore unable to reveal the disposition of individual enantiomers. Consequently, the occurrence of any enantiomeric interaction(s) may remain undetected. As previously pointed out by others [16-18], conclusions regarding disposition of chiral compounds can only be made after examining enantiomeric disposition. Our laboratory has recently reported the stereospecific pharmacokinetics of sotalol in humans [19] using a stereospecific assay [20], and found that there were no significant differences between the two enantiomers of sotalol after racemate administration. However, we were unable to administer both pure sotalol enantiomers to humans, as their use in humans had not been approved.

As it is known that the enantiomers of other drugs administered as the racemate may interact with one another [21-24], it was hypothesized that an enantiomeric interaction may also exist with sotalol despite the similar time-course of the enantiomers after racemate administration in humans. The existence of such an interaction may especially be of clinical importance, as sotalol may be administered as either the racemate or pure S-enantiomer depending on the indication for use. In more

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practical terms, therefore, the disposition of sotalol enantiomers may differ depending on the clinical indication for its use. Consequently, the present study undertook to study the enantiomeric disposition after administration of racemate and pure enantiomer. As administration of both the pure R- and S-sotalol enantiomers in humans had not yet been approved, the Sprague-Dawley rat was chosen for evaluation as a suitable animal model.

Materials and Methods

Chemicals

Racemic, S-, and R-sotalol were gifts from Bristol-Myers Squibb (Ottawa, Ontario, Canada). The internal standard (I.S.), racemic atenolol, was obtained from ICI Pharma (Mississauga, Ontario, Canada). All other chemicals and reagents were HPLC or analytical grade.

Surgery and Animal Maintenance

Male Sprague-Dawley rats weighing between approximately 200 and 500 g were used for the study. A total of 18 rats were catheterized with silastic tubing (0.025" i.d. X 0.037" o.d.; Dow Corning, Midland, MI, U.S.A.) at the right jugular vein. Immediately prior to, and during surgery, rats were anesthetized *via* inhalation of methoxyflurane (Pitman-Moore Ltd., Mississauga, Canada). The animals were allowed to recover overnight prior to the experiment. During this time the animals were individually stored in 18" X 9.5" X 8" polycarbonate rodent cages, fasted and given water *ad libitum*.

Drug Administration and Sample Collection

Racemic, S-, or R-sotalol dissolved in normal saline were administered (5 mg/kg of each enantiomer) *via* the jugular vein cannula. After administration of the sotalol dose, the cannula was flushed with approximately 1.0 ml of normal saline. Blood (0.25 ml) was collected from the jugular vein cannula just prior to, and at 0.25,

0.5, 0.75, 1, 1.5, 2, 3, 4, and 6 h after drug administration. Between each blood sample collection 0.2 ml normal (0.9%) saline was administered *via* the jugular vein cannula as fluid replacement, and the cannula was heparinized (10 U/ml). Blood samples were centrifuged and the plasma portion was separated and immediately frozen at -20° C until analyzed. Animals were given water *ad libitum* throughout the study and food was withheld only during the two h period immediately following drug administration.

Urine was collected and pooled for 24 h following drug administration. Urine samples were kept frozen at -20° C until just prior to analysis.

Stereospecific HPLC Analysis of Sotalol

Concentrations of S- and R-sotalol in plasma and in urine were determined utilizing a previously reported stereospecific HPLC method [20]. Urine samples were diluted 1:100 (v/v) in HPLC water prior to stereospecific analysis for sotalol.

Pharmacokinetic Data Analysis

The area under the plasma concentration-time curve (AUC) was calculated by the log trapezoidal rule. The area from the last concentration point (C_{last}) to infinity was calculated as C_{last}/λ_n, where λ_n was the terminal elimination rate constant. Either the terminal 3, 4, or 5 (based on visual inspection) plasma concentration-time curve points were used in the determination of λ_n. The terminal half-life of elimination ($t_{1/2}$) was determined as $0.693/\lambda_n$. Systemic clearance (Cl) was calculated as D/AUC, where D was the enantiomeric dose administered and AUC was the corresponding area under the plasma enantiomer concentration-time curve. The mean residence time (MRT) for each enantiomer was determined for each subject using a Lagran computer software program [25]. Volume of distribution at steady-state (Vd_{ss}) was calculated by multiplying Cl and MRT. Mean plasma concentration-time plots were generated for display purposes only by fitting the data to tri-exponential functions. As sotalol urinary excretion was virtually 100% in 24 h, renal clearance (Cl_r) was estimated by

dividing the cumulative 24 h urinary excretion of each sotalol enantiomer by the corresponding AUC (0 - inf.) value.

Statistical Analysis

Comparisons between the S- and R-sotalol concentrations observed in rats administered the racemate were assessed utilizing a Student's *t* test for paired data. All other comparisons of enantiomer concentration were assessed by an independent measures Student's *t* test. All *t* tests were two-tailed, with the level of significance pre-set a $\alpha = 0.05$. Results are expressed as mean ± SD.

Results

Following administration of racemic sotalol, the R- and S-enantiomer plasma concentration-time curves were virtually superimposed (Figure 4-1). As expected, therefore, statistically significant pharmacokinetic differences between the two enantiomers were not observed following administration of the racemate. The pharmacokinetic parameters are summarized in Table 4-1.

The enantiomer plasma concentration-time curves for S- and R-sotalol after administration of the pure enantiomers, compared with the same enantiomer after racemate administration, are presented in Figures 4-2 and 4-3, respectively. When S-sotalol was administered alone, plasma concentrations were greater than when the racemate was administered (Figure 4-2). Hence, as summarized in Table 4-1, the AUC of S-sotalol was significantly greater after pure enantiomer, compared to racemate, administration. Cl_s and Cl_r values, normalized for body weight, following administration of the pure S-sotalol enantiomer were significantly reduced, and the elimination $t_{1/2}$ was prolonged, compared to administration as racemate.

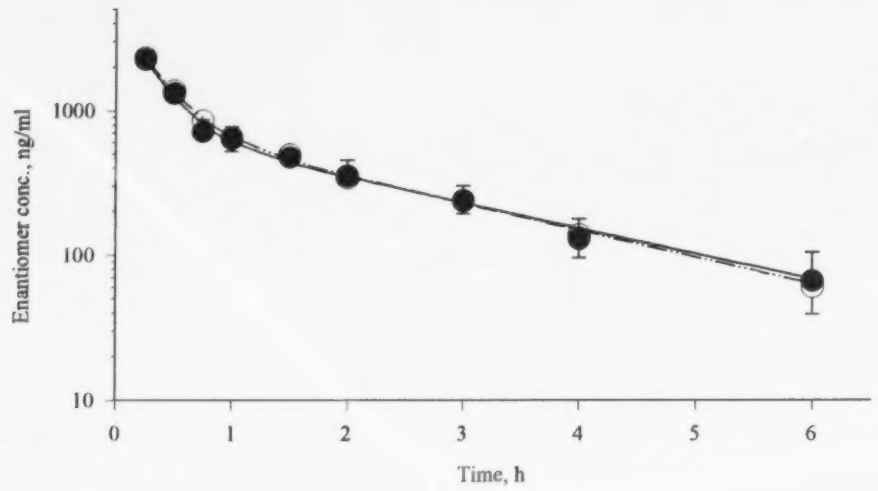

Figure 4-1. Average plasma concentration versus time profiles for S- and R-sotalol after administration of the racemate. S-sotalol = open circles; R-sotalol = filled circles; dashed line = the tri-exponential function that best fits the data for S-sotalol; solid line = the tri-exponential function that best fits the data for R-sotalol; error bars represent SD.

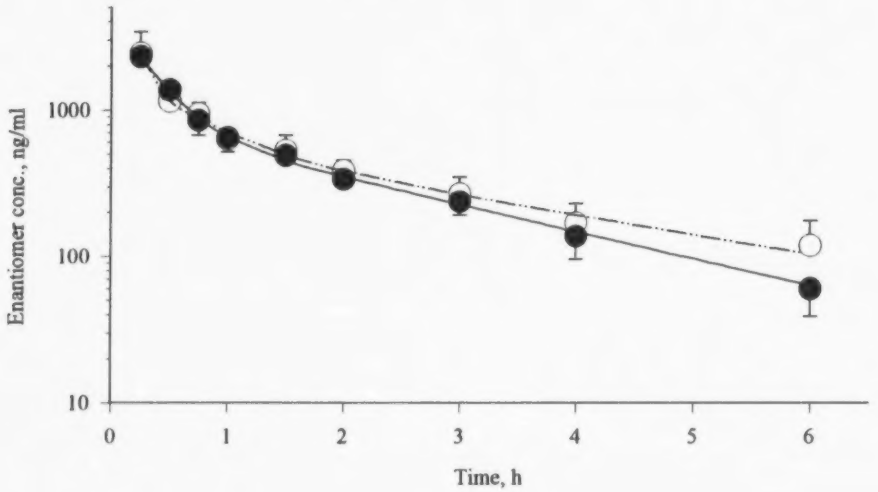

Figure 4-2. Average plasma concentration versus time profiles for S-sotalol after racemate and pure enantiomer administration. S-sotalol after pure enantiomer = open circles; S-sotalol after racemate = filled circles; dashed and solid lines represent the tri-exponential functions that best fit the data for administration as pure enantiomer and racemate, respectively; error bars represent SD.

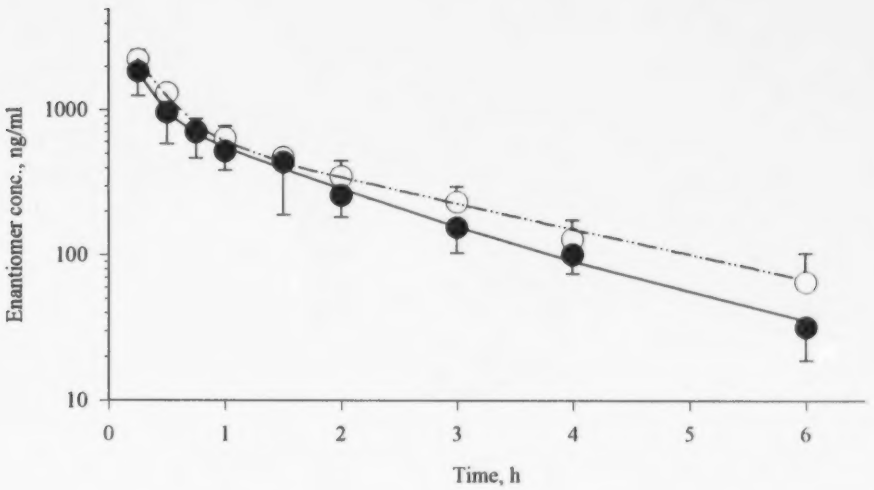

Figure 4-3. Average plasma concentration versus time profiles for R-sotalol after racemate and pure enantiomer administration. R-sotalol after racemate = open circles; R-sotalol after pure enantiomer = filled circles; dashed and solid lines represent the tri-exponential functions that best fit the data for administration as racemate and pure enantiomer, respectively; error bars represent SD.

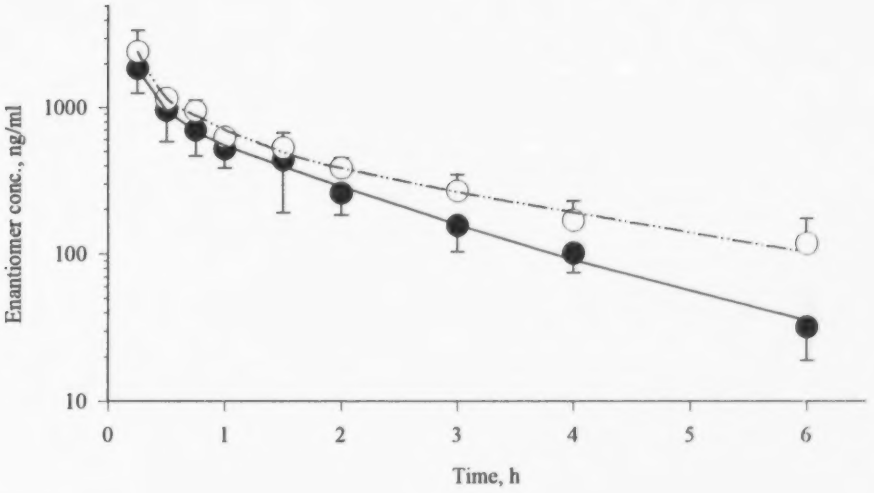

Figure 4-4. Average plasma concentration versus time profiles for S- and R-sotalol after administration of pure enantiomers. S-sotalol = open circles; R-sotalol = filled circles; dashed line = the tri-exponential function that best fits the data for S-sotalol; solid line = the tri-exponential function that best fits the data for R-sotalol; error bars represent SD.

Table 4-1. Pharmacokinetic characteristics of sotalol after administration as (a) racemate and (b) pure enantiomer to rats (n = 18).

(a)

Rat	Weight, g		$AUC_{0\text{-}inf.}$, (ng/ml)*h		$t_{1/2}$, h		Cls, ml/min/kg		Clr, ml/min/kg		% recovered in urine		MRT, h		Vdss, l/kg	
			S	R	S	R	S	R	S	R	S	R	S	R	S	R
1	510		2378	2095	1.61	1.63	35.0	39.9	25.6	29.7	73	75	2.35	2.28	4.94	5.45
2	470		2251	1521	1.94	1.16	36.9	54.6	31.1	46.0	84	84	2.48	1.51	5.51	4.96
3	240		1874	2061	1.31	1.82	44.4	40.4	42.6	36.2	96	98	1.91	2.20	5.08	5.33
4	280		2191	2204	1 61	1.77	38.0	37.8	30.4	28.7	85	83	2.01	2.16	4.57	4.89
5	270		2021	2794	1.09	1.99	41.2	29.8	36.7	25.3	79	83	1.96	1.88	4.93	5.13
6	300		2391	2182	1.27	1.13	42.8	45.8	35.9	37.1	93	85	1.96	1.88	4.93	5.13
Mean:	345		2184†	2143	1.47†	1.58	39.7†	41.4	33.7†	33.9	83	85	2.05	2.12	4.83	5.10
SD:	115		204	406	0.31	0.36	3.7	8.3	6.0	7.5	9	8	0.32	0.40	0.52	0.25

(b)

Rat	Weight, g		$AUC_{0\text{-}inf.}$, (ng/ml)*h		$t_{1/2}$, h		Cls, ml/min/kg		Clr, ml/min/kg		% recovered in urine		MRT, h		Vdss, l/kg	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
1	280	300	2056	2418	1.75	1.18	40.5	34.4	32.8	27.9	84	81	2.19	1.61	5.32	3.33
2	300	260	3294	1132	1.15	1.74	25.3	73.7	22.5	65.6	88	91	1.72	1.96	2.60	8.65
3	210	320	2249	1523	2.52	2.39	37.1	54.7	31.5	46.5	86	85	2.58	2.89	5.71	9.47
4	470	425	3173	1616	4.55	0.93	26.3	51.8	22.7	42.5	86	82	5.37	1.54	8.47	4.78
5	490	445	3290	1994	3.15	1.30	25.3	42.0	19.7	34.2	78	82	4.06	1.97	6.18	4.94
6	470	434	3294	1501	3.10	1.70	23.9	55.3	21.4	50.2	90	90	4.03	2.12	5.77	7.10
Mean:	370	364	2893‡	1697	2.70	1.54	29.7‡	52.0	28.9‡	46.7	84	84	3.33	2.02	5.68	6.38
SD:	121	80	578	448	1.19	0.52	7.2	13.4	5.6	18.9	4	4	1.39	0.48	1.88	2.41

† Significantly different from corresponding enantiomer administered alone, $p < 0.05$.

‡ Significantly different from R-sotalol administered alone, $p < 0.05$.

Figure 4-3 depicts the enantiomer plasma concentration-time profile of R-sotalol after administration as the pure enantiomer or racemate. Although there was a trend of greater plasma concentrations of R-sotalol after administration of the racemate, these differences did not achieve statistical significance. The pharmacokinetic parameters determined for R-sotalol are summarized in Table 4-1. Although there were no significant differences between R- and S-sotalol disposition after administration of racemate, significant differences in AUC, Cl_s, and Cl_r were observed between R- and S-sotalol after administration of pure enantiomer (Figure 4-4 and Table 4-1).

Extrapolated AUC ($AUC_{6h\text{-}inf.}$) represented, on average, 7.7% of the total AUC ($AUC_{0\text{-}inf.}$).

There were no significant differences between mean rat weights between groups given racemic sotalol, or either S- or R-sotalol.

Discussion

There are numerous examples in the literature describing the varying pharmacologic properties of enantiomers [18,26]. With sotalol, these enantioselective pharmacologic differences are useful clinically, where the racemate is administered in the treatment of hypertension; pure S-sotalol is administered as a class III antiarrhythmic. Thus, the enantiomeric time-course must be clearly delineated after either racemate or pure enantiomer administration, as the indication for use necessitates administration of either racemate or enantiomer. Moreover, as it is known that the enantiomers of other chiral drugs such as terbutaline [24], disopyramide [23], and 5-dimethylsulfamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid (DBCA) [27] interact with one another, conclusions regarding enantiomer disposition after racemate administration must not be extrapolated to the expected disposition following enantiomer administration.

We previously reported the enantiomeric disposition of sotalol following administration of the racemate to humans [19]. In this study, it was concluded that the

disposition of sotalol was not stereoselective. Consequently, it may be concluded that as stereoselective disposition processes were not readily apparent, there may be little reason to expect that enantioselective processes would occur following pure enantiomer administration. To test the hypothesis that stereoselective processes may nevertheless exist, the enantiomeric disposition of sotalol was investigated after both racemate and enantiomer administration. To conduct this test, the Sprague-Dawley rat was chosen as an animal model, as regulatory approval for administration of both pure enantiomers to humans was not readily feasible. Additionally, the use of the Sprague-Dawley rat was deemed suitable as, in man, the disposition of sotalol enantiomers following racemate administration was not stereoselective and the drug was excreted mainly intact in urine.

Administration as the Racemate

After administration of the racemate, the pharmacokinetics of S- and R-sotalol in rats was not stereoselective. The absence of stereoselectivity should, perhaps, be expected for a number of reasons. Firstly, doses were administered intravenously, thereby precluding stereoselective absorption or presystemic metabolism. Secondly, as sotalol is relatively hydrophilic compared with many other β-blockers and is excreted virtually entirely as intact drug in urine [1,3,28], stereoselective hepatic metabolism is not likely. Stereoselective metabolism occurs, however, with the less hydrophilic β-blockers including, for example, propranolol [26,29] and metoprolol [30]. Finally, as plasma protein binding was minimal for sotalol enantiomers in rat (unpublished data) and as enantiomer renal clearance values were similar, distribution and excretion differences were not likely.

Although plasma concentrations of S- and R-sotalol were not significantly different following racemate administration, consideration was given to the possible occurrence of an enantiomeric interaction despite the observed non-stereoselective profile obtained after racemate. Such a finding is theoretically possible either as a consequence of a pharmacodynamic or pharmacokinetic enantiomeric interaction. For example, a pharmacodynamic interaction between enantiomers may exist if the

pharmacologic effect associated with one enantiomer influences the physiological process(es) by which the other enantiomer is handled. An interaction of this nature has previously been shown for propranolol where S-propranolol decreased the clearance of both enantiomers by decreasing hepatic blood flow [31]. Alternatively, an enantiomeric interaction may occur as a result of pharmacokinetic processes including for example, drugs that compete for protein binding sites (e.g., ibuprofen, disopyramide) or drugs competing for active transport mechanisms (e.g., terbutaline, 5-dimethylsulfamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid (DBCA)) [21,27].

Administration as the Pure Enantiomer

The AUC values for S-sotalol that were obtained after administration of pure S-sotalol were significantly greater than when given as the racemate. Consequently, the Cl_s of S-sotalol was significantly reduced after administration of the pure enantiomer (29.7 ± 7.2 ml/min/kg) when compared with administration of racemate (39.7 ± 3.7 ml/min/kg). Additionally, the $t_{1/2}$ was significantly prolonged after administration of pure S-sotalol (2.70 ± 1.19 h) compared with racemate (1.47 ± 0.31 h). It was noted that the observed difference in $t_{1/2}$ resulted in extrapolated AUC ($AUC_{6h\text{-}inf.}$) values which contributed 5.8% and 12.5% to the total AUC ($AUC_{0\text{-}inf.}$) values for S-sotalol administered as the racemate or pure enantiomer, respectively. This difference in the magnitude of the extrapolated AUC values contributed to the observed significant difference ($p = 0.0181$) in total AUC values between sotalol administered as racemate or pure enantiomer. When only the partial AUC values ($AUC_{0\text{-}6h}$) were compared, the difference between S-sotalol administered as racemate and pure enantiomer approached, but did not achieve significance ($p = 0.0587$). The partial AUC values for S- and R-sotalol administered as pure enantiomers were, however, significantly different ($p = 0.00888$). As in all cases the extrapolated AUC contributed less than 13% to the total AUC, and as the terminal elimination phase of the log concentration *versus* time data were well-fitted to linear decline, the calculation of total AUC values was deemed appropriate. Values for volume of distribution were

not significantly altered for either enantiomer when racemate and pure enantiomer administration were compared.

The observed differences in Cl_s of S-sotalol when administered either as racemate or pure enantiomer corresponded to differences in Cl_r (33.7 ± 6.0 and 28.9 ± 5.6 ml/min/kg, for S-sotalol administered as racemate and pure enantiomer, respectively). As expected, therefore, the Cl_s correlated with Cl_r (e.g., $r^2 = 0.96$ for Cl_r *versus* Cl_s for S-sotalol after pure enantiomer administration). Interestingly, the Cl_r of sotalol enantiomers ranged from approximately three-times the reported glomerular filtration rate (GFR) values [32] when pure S-sotalol was administered to approximately five-times the GFR when pure R-sotalol was administered. When sotalol was administered as the racemate, the Cl_r of both sotalol enantiomers was approximately four-times GFR. This contrasts sharply to the renal excretion of sotalol in dogs [33,34] where Cl_r is attributable mainly to glomerular filtration. In the present study, it appeared that the Cl_r of sotalol enantiomers was *via* glomerular filtration with tubular secretion contributing to a significant extent in the overall Cl_r. Furthermore, it appeared that the clearance of S-sotalol was enhanced when R-sotalol was present (administration as the racemate).

Studies have determined both renal plasma flow and renal blood flow in the rat [35,36,37,38]. Based on these studies, reported flow values were variable and ranged up to approximately 55-60 ml/min/kg for renal blood flow. As Cl_s and Cl_r values were similar, and both approached the reported values for renal blood flow, changes in the Cl_r of S-sotalol in the presence of R-sotalol were most likely renal perfusion-dependent. Changes in Cl_r of S-sotalol after administration of either racemate or pure enantiomer is largely dependent, therefore, on blood flow and less dependent on changes in extraction (i.e., renal transport). Changes in renal perfusion caused by the presence of the β-blocking properties of R-sotalol is likely, therefore, to have a pharmacodynamic basis.

A pharmacodynamic interaction between the enantiomers of sotalol is feasible given the greater β-blocking potency of R-sotalol compared with S-sotalol [3]. In the present study, β-blockade was more prominent when the racemate or pure R-

enantiomer were administered, but not when pure S-sotalol was given. The exact nature of perfusion changes remains to be examined, as the renal perfusion effects of other β-blockers including celiprolol, nadolol, atenolol, and propranolol are varied [39].

In conclusion, this study serves to underscore the importance of examining the enantiomeric disposition of drugs administered as racemates. This is especially true when attempting to compare the pharmacokinetics of a pure enantiomer with the pharmacokinetics of the same enantiomer administered as a racemate. When stereospecific studies are neglected, attempts to extrapolate drug disposition data collected after racemate administration to the disposition of the enantiomer (or vice versa) are meaningless and may lead to incomplete conclusions. The pharmacokinetics of sotalol in the present study indicated that, similar to humans, S- and R-sotalol plasma concentrations collected from the Sprague-Dawley rat after administration as racemate were superimposable. Interestingly, administration of the pure S-enantiomer resulted in significantly reduced systemic clearance values compared to when the racemate was administered. It was suggested that the reduction in systemic, and renal, clearance resulted from a pharmacodynamic enantiomeric interaction. Although the disposition of S-sotalol was significantly altered in the presence of R-sotalol, conclusions regarding the clinical significance of this interaction require further testing in patient groups.

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➢ CHAPTER 5 ≺

Influence of Cimetidine Co-administration on the Pharmacokinetics of Sotalol Enantiomers in an Anesthetized Rat Model: Evidence Supporting Active Renal Excretion of Sotalol♦

Introduction

Despite the differing pharmacology between enantiomers [1-6], only recently have stereospecific studies been published on sotalol pharmacokinetics in humans [7,8], and in rat model [9]. In healthy, young male human adults (mean age 32 y) no stereoselectivity in disposition was observed following a single oral sotalol dose, whereas in older male and female patients with supraventricular arrhythmias (mean age 60 y), modest but significant stereoselectivity (R > S) was noted with oral clearance, renal clearance, non-renal clearance, and fraction unbound to plasma proteins after steady-state sotalol dosing. Sotalol enantiomers are primarily eliminated intact *via* renal excretion, and in both humans [7,8] and rat model [9], renal clearance values (Cl_r) for enantiomers substantially exceed glomerular filtration rate (GFR). Although it is likely that active process(es) are involved in the renal elimination of sotalol enantiomers, the existence and nature of these process(es) has not yet been investigated.

Mechanisms involved in the renal elimination of xenobiotics from the body include the passive process of glomerular filtration, and active processes of tubular secretion and tubular reabsorption. As Cl_r exceeds GFR, it is reasonable to suggest that sotalol enantiomers are excreted by glomerular filtration in combination with tubular secretion. It is also possible that some degree of tubular reabsorption also occurs, although the net effect would favor secretion. There appear to be at least two

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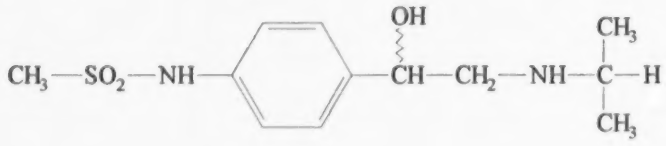
discrete tubular secretion mechanisms, including one for cations and one for anions. These mechanisms appear to be relatively specific [10-12], although it has been proposed that cimetidine has both a high affinity for the cation transport system and a low affinity for the anion transport system [13]. Zwitterionic drugs such as sotalol enantiomers and many cephalosporin antibiotics could, in theory, interact with both cationic and anionic secretory mechanisms. It has, however, been calculated that at pH 7.4 the proportion of sotalol enantiomers in the zwitterionic form is approximately only 10% [14,15].

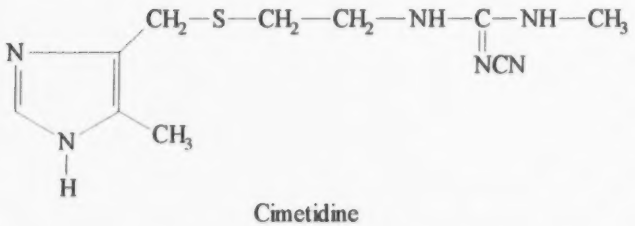
The extent to which zwitterions are renally excreted *via* the anionic or cationic mechanisms is likely dependent, in part, upon the relative extent of ionization of the acidic and basic moieties, as only the ionic species is actively secreted across the proximal tubule. Cephalexin, for example, contains a carboxyl group (pKa, 2.7) which is completely ionized at blood pH, and an amino group (pKa, 7.0) that is approximately one-third ionized. The results from human studies [11,16] suggests that although cephalexin tubular secretion is mediated by both anionic and cationic secretory mechanisms, tubular secretion is less affected by inhibition of the cationic transporter than the anionic transporter. This would be consistent with the relative fraction of the total ionized molecule existing in the cationic state. Applying the same rationale to sotalol enantiomers, it is expected that the secondary amine (pKa, 9.8) would be ionized to a greater extent than the sulfonamide (pKa, 8.3) functionality, (99.7 *versus* < 10%, respectively). It is proposed, therefore, that tubular secretion of sotalol enantiomers would be mediated by the cationic renal transporter.

In this paper, the nature of the renal elimination process of sotalol enantiomers is investigated by addressing the hypothesis that sotalol enantiomers are excreted *via* an active organic cation transporter in the renal tubules. To test for the presence of an active organic cation transport system, cimetidine is co-administered with racemic sotalol in a Sprague-Dawley rat model, as cimetidine co-administration has been shown to be useful in investigating the nature of renal excretion of drugs [11,13,17]. The chemical structures of sotalol and cimetidine are presented in Figure 5-1. Cimetidine reduces Cl_r of certain basic drugs *via* a relatively selective inhibition of a

common cationic secretory transport mechanism in the proximal tubule, rather than *via* a nonspecific action on renal function [11]. Although cimetidine inhibits microsomal P450 enzymes, such effects would not be expected to affect sotalol disposition, as sotalol is not metabolized [5,18]. As cimetidine has a short $t_{1/2}$ in rat (approximately 45 min, [19]), and tubular secretion interactions with cimetidine have been reported to be dependent on cimetidine plasma concentration [11], the effects of either single dose or constant infusion of cimetidine on sotalol enantiomer pharmacokinetics are presented. Such information may be useful in identifying and predicting certain drug-drug interactions.



Sotalol



Cimetidine

Figure 5-1. Chemical structures of sotalol and cimetidine.

Materials and Methods

Chemicals

Racemic sotalol (Figure 5-1) was a gift from Bristol-Myers Squibb (Ottawa, Ontario, Canada). Cimetidine (Figure 5-1) was obtained from Sigma Chemical Co. (St. Louis, MO, U.S.A.). All other chemicals and reagents were HPLC or analytical grade.

Surgery and Animal Maintenance

Male Sprague-Dawley rats weighing between approximately 300 and 400 g were used for the study. A total of 26 rats were catheterized with silastic tubing (0.025" i.d. X 0.037" o.d.; Dow Corning, Midland, MI, U.S.A.) at the right jugular vein. Prior to surgery and throughout the study, rats were anesthetized *via* intraperitoneal sodium pentobarbital (M.T.C. Pharmaceuticals, Cambridge, Ontario, Canada), dosed at 40 mg/kg initially, then 10 mg/kg intraperitoneally as required to maintain anesthesia.

Drug Administration and Sample Collection

All rats were administered 5 mg/kg of each enantiomer of sotalol dissolved in normal (0.9%) saline as a bolus at the beginning of the study (time zero). Also at time zero, rats were administered either a bolus of 30 mg/kg cimetidine in normal saline (cimetidine bolus group, n = 7), normal saline bolus (saline bolus group, n = 6), 30 mg/kg cimetidine bolus plus cimetidine infusion of 50 mg/kg in 5 ml normal saline over 6 h (cimetidine infusion group, n = 7), or normal saline bolus plus normal saline infusion of 5 ml over 6 h (saline infusion group, n = 6). Sotalol and cimetidine bolus dosing solutions were prepared at concentrations of 5 mg/ml of each enantiomer, and 30 mg/ml, respectively. Blood (0.25 ml) was collected from the jugular vein cannula just prior to, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 h after drug administration. For both saline bolus and cimetidine bolus-dosed groups, 0.25 ml normal saline was administered *via* the jugular vein cannula between each blood sample collection as fluid replacement. Blood samples were immediately centrifuged and the plasma portion was separated and immediately frozen at -20° C until analyzed.

Urine was collected during the study *via* a PVC plastic cannula placed under the foreskin of the penis, and was pooled with urine taken directly from the bladder *via* syringe aspiration at the termination of the study (6 h). Urine samples were kept frozen at -20° C until just prior to analysis.

Stereospecific HPLC Analysis of Sotalol

Concentration of S- and R-sotalol in plasma and in urine were determined utilizing a validated and previously reported stereospecific HPLC method [20]. Urine samples were diluted 1:100 (v/v) in HPLC water prior to stereospecific analysis for sotalol.

Pharmacokinetic Data Analysis

The plasma concentration-time data of sotalol enantiomers were fitted to bi-exponential functions. Nonlinear regression analysis was performed using PCNONLIN software (Gauss-Newton algorithm with the Levenberg modification, [21]). Since the relative error of the HPLC assay method was somewhat larger at the low concentrations [20], the weighting factor $1/C_{calc}$ was used for the curve-fitting analysis, where C_{calc} was the concentration calculated by PCNONLIN. Area under the plasma concentration-time curve ($AUC_{0\text{-}inf.}$) was calculated as $A/\alpha + B/\beta$, where A and B are the extrapolated concentrations at time 0 for distribution and elimination phases, respectively, and α and β are elimination rate constants for the distribution and elimination phases, respectively. Area under the plasma concentration-time curve from time 0 to 6 h ($AUC_{0\text{-}6h}$) was calculated as $AUC_{0\text{-}inf.} - C_{6h}/\beta$, where C_{6h} is the sotalol enantiomer plasma concentration at 6 h post-dose. Systemic clearance (Cl_s) was calculated as $D/AUC_{0\text{-}inf.}$, where D was the enantiomeric dose administered and $AUC_{0\text{-}inf.}$ was the corresponding area under the plasma enantiomer concentration-time curve. Urinary clearance (Cl_r) of sotalol enantiomers was estimated by dividing the cumulative 6 h urinary excretion ($\Sigma Xu_{0\text{-}6h}$) of each sotalol enantiomer by the corresponding $AUC_{0\text{-}6h}$ value. The fraction of dose excreted unchanged in the urine over the 6 h study period, ($Ae_{0\text{-}6h}\%$), was calculated as $100*\Sigma Xu_{0\text{-}6h}/D$. Non-renal clearance ($Cl_{nr}$) was calculated as $Cl_s - Cl_r$. Mean residence time (MRT) was calculated as AUMC/AUC, where AUMC is the area under the first moment curve calculated by PCNONLIN. Volume of distribution at steady-state (Vd_{ss}) was calculated as Cl_s*MRT. Elimination half-life ($t_{1/2\beta}$) was calculated as $0.693/\beta$.

Statistical Analysis

Statistical comparisons of the pharmacokinetic parameters of S- *versus* S-sotalol and R- *versus* R-sotalol between groups were made by one-way ANOVA followed by Scheffé's post-hoc test. Potential interaction between group and S/R ratio was assessed for each pharmacokinetic parameter by computing S/R ratios for each rat, then comparing S/R ratios between groups using ANOVA as above. Assumptions of normality and homogeneity of variance were tested using the Lilliefors and Levene tests [22], respectively, prior to ANOVA analysis. Comparisons between the S- and R-sotalol pharmacokinetic parameters within each study group were assessed utilizing a two-tailed Student's *t* test for paired data. To control for type I error, the Bonferonni procedure was used in setting the pairwise $\alpha = 0.0125$ (0.05/4 groups). In all other tests, a probability level < 0.05 was considered statistically significant.

Results

Average plasma concentration *versus* time curves, after administration of racemic sotalol for saline and cimetidine bolus groups, are presented for S-sotalol (Figure 5-2) and R-sotalol (Figure 5-3). Average plasma concentration *versus* time curves, after administration of racemic sotalol for saline and cimetidine infusion groups, are presented for S-sotalol (Figure 5-4) and R-sotalol (Figure 5-5). The data were well-fitted to bi-exponential functions (Figures 5-2 through 5-5).

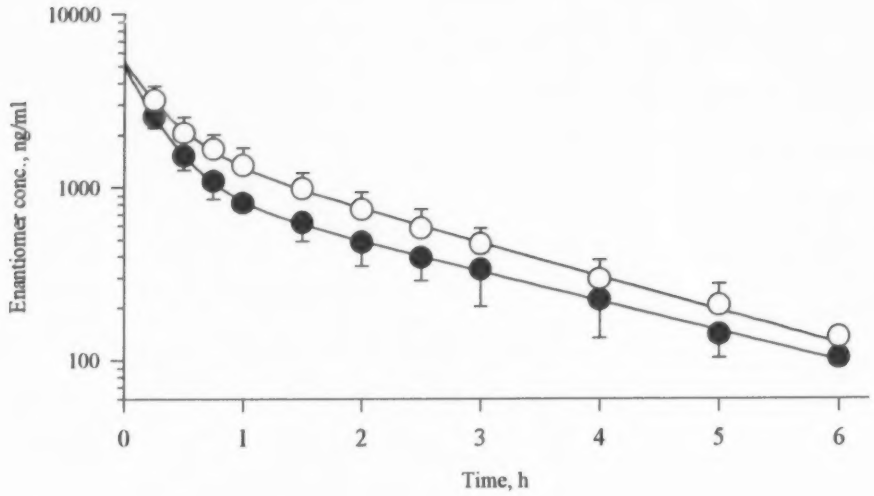


Figure 5-2. The average plasma concentration versus time profiles for S-sotalol after administration of the racemate for bolus cimetidine and bolus saline groups. S-sotalol after cimetidine bolus = open circles; S-sotalol after saline bolus = filled circles; solid lines are the bi-exponential functions that best fit the data; error bars represent SD.

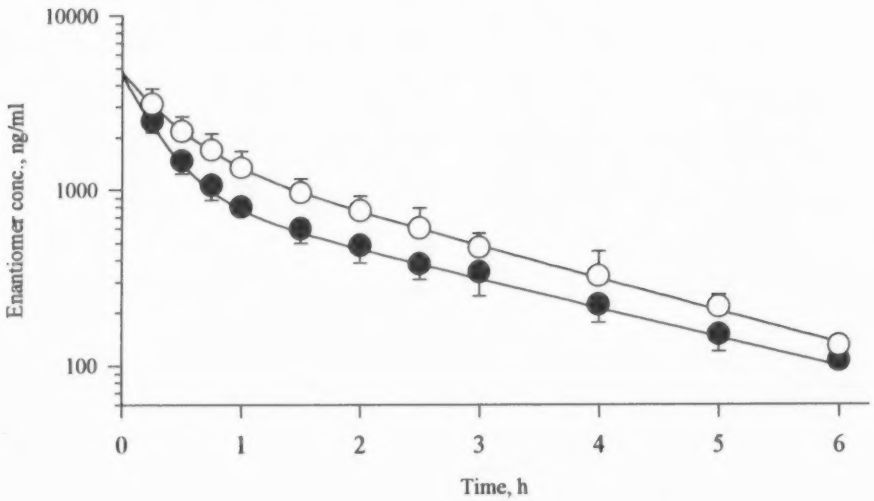


Figure 5-3. The average plasma concentration versus time profiles for R-sotalol after administration of the racemate for bolus cimetidine and bolus saline groups. R-sotalol after cimetidine bolus = open circles; R-sotalol after saline bolus = filled circles; solid lines are the bi-exponential functions that best fit the data; error bars represent SD.

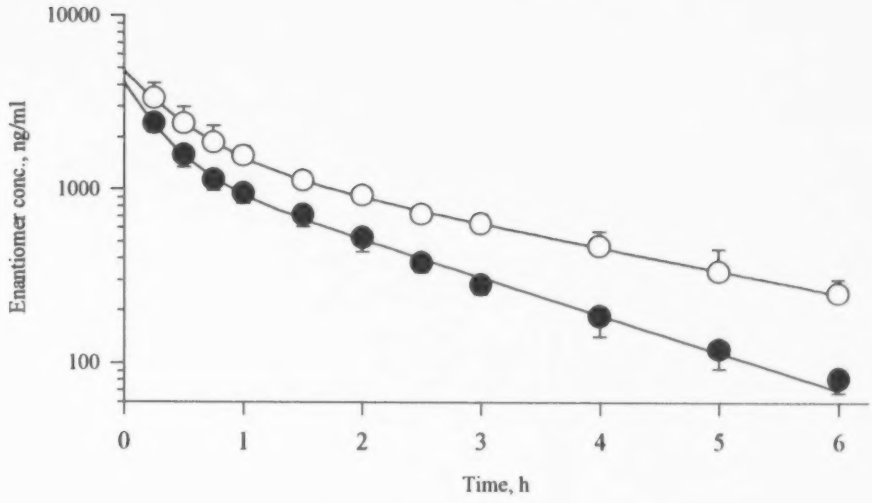


Figure 5-4. The average plasma concentration versus time profiles for S-sotalol after administration of the racemate for cimetidine infusion and saline infusion groups. S-sotalol after cimetidine infusion = open circles; S-sotalol after saline infusion = filled circles; solid lines are the bi-exponential functions that best fit the data; error bars represent SD.

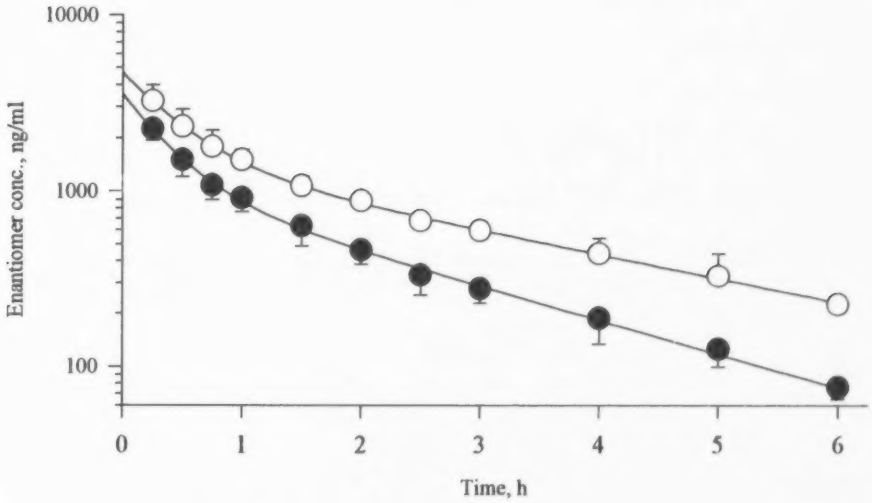


Figure 5-5. The average plasma concentration versus time profiles for R-sotalol after administration of the racemate for cimetidine infusion and saline infusion groups. R-sotalol after cimetidine infusion = open circles; R-sotalol after saline infusion = filled circles; solid lines are the bi-exponential functions that best fit the data; error bars represent SD.

Rats administered cimetidine as an intravenous bolus, when compared with saline bolus controls, showed a significant reduction in Cl_r of both sotalol enantiomers. As a result, the cimetidine group showed significantly greater AUCs, as well as significantly reduced Cl_s and $\Sigma Xu_{0\text{-}6h}/D$ of sotalol enantiomers when compared to controls. There was no difference in Cl_{nr}, Vd_{ss}, MRT, or $t_{1/2\beta}$ between the two groups. The pharmacokinetic parameters of sotalol enantiomers in saline and cimetidine bolus groups are summarized in Table 5-1.

As was seen in the bolus groups, rats administered cimetidine as an intravenous infusion showed significant reductions in Cl_r and Cl_s, and therefore a significant increase in AUCs of both sotalol enantiomers when compared with saline infusion controls. The magnitude of the differences in these parameters was greater for the infusion groups than the bolus groups. Similar to the bolus groups, there were no significant differences in Vd_{ss} or Cl_{nr} between cimetidine infusion and control groups. Unlike the cimetidine bolus group, however, the cimetidine infusion group showed increased $t_{1/2\beta}$ of sotalol enantiomers compared with respective saline controls. The pharmacokinetic parameters of sotalol enantiomers in saline and cimetidine infusion groups are summarized in Table 5-1.

A modest, but statistically significant, stereoselectivity in sotalol disposition was observed in the cimetidine infusion group. In this group, Cl_s of R-sotalol was significantly greater than for S-sotalol, resulting in significantly larger AUC values (both total and partial) for S-sotalol. The magnitude of stereoselectivity was less than 5%. There were no significant differences between groups in S/R ratio for any of the pharmacokinetic parameters reported.

Results from Levene and Lillifores tests confirmed the normality and homogeneity-of-variance assumptions for the pharmacokinetic data of each parameter reported.

Table 5-1. Pharmacokinetic characteristics. Data are presented as mean (SD).

Pharmacokinetic	*Saline Bolus*		*Cimetidine Bolus*		*Saline Infusion*		*Cimetidine Infusion*	
Parameters	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*
$AUC_{0\text{-}inf.}$, ng*h/ml	3787^{bd}	3749^{bd}	5175^{acd}	5252^{acd}	3657^{bd}	3434^{bd}	6754^{*abc}	6458^{*abc}
	(617)	(390)	(953)	(874)	(409)	(504)	(535)	(634)
$AUC_{0\text{-}6h}$, ng*h/ml	3546^{bd}	3481^{bd}	4893^{ac}	4924^{ac}	3522^{bd}	3272^{bd}	5880^{*ac}	5636^{*ac}
	(581)	(400)	(935)	(865)	(393)	(504)	(428)	(527)
Cls, ml/min/kg	22.5^{bd}	22.4^{bd}	16.5^{ac}	16.2^{ac}	23.0^{bd}	24.7^{bd}	12.4^{*ac}	13.0^{*ac}
	(3.7)	(2.2)	(2.8)	(2.3)	(2.6)	(3.7)	(1.0)	(1.2)
Clr, ml/min/kg	17.7^{bd}	18.2^{bd}	10.4^{ac}	10.0^{ac}	18.1^{bd}	19.7^{bd}	7.61^{ac}	7.95^{ac}
	(3.4)	(2.3)	(1.7)	(1.5)	(2.9)	(4.1)	(1.0)	(1.2)
Clnr, ml/min/kg	4.83	4.18	6.09	6.20	4.92	5.06	4.78	5.04
	(1.5)	(1.6)	(2.1)	(1.5)	(1.1)	(1.5)	(0.9)	(1.3)
$Ae_{0\text{-}6h}$%	73.5^{*bd}	75.6^{*bd}	60.0^{ac}	57.8^{ac}	75.5^{bd}	75.2^{bd}	53.9^{ac}	53.7^{ac}
	(7.3)	(7.1)	(7.2)	(4.6)	(4.7)	(5.2)	(8.5)	(8.4)
Vdss, ml/kg	2450	2611	1803	1866	2174	2504	1974	2054
	(534)	(581)	(356)	(352)	(318)	(491)	(615)	(612)
MRT, h	1.82	1.94	1.82	1.92	1.57^{d}	1.69^{d}	2.69^{c}	2.67^{c}
	(0.33)	(0.36)	(0.30)	(0.27)	(0.16)	(0.22)	(0.98)	(0.86)
$t_{1/2\beta}$, h	1.72	1.80	1.56^{*d}	1.66^{*}	1.37^{d}	1.53^{d}	2.25^{bc}	2.25^{c}
	(0.27)	(0.33)	(0.26)	(0.25)	(0.17)	(0.25)	(0.68)	(0.62)
Rat weight, g	357		354		314		322	
	(32)		(32)		(20)		(34)	

$AUC_{0\text{-}inf.}$, area under the plasma concentration-time curve from zero to infinity; $AUC_{0\text{-}6h}$, area under the plasma concentration-time curve from zero to 6 h; Cls, systemic clearance; Clr, renal clearance; Clnr, non-renal clearance; $Ae_{0\text{-}6h}$%, fraction of dose excreted unchanged in urine during the 6 h study period; Vdss, volume of distribution at steady-state; MRT, mean residence time; $t_{1/2\beta}$ half-life of the elimination phase.

[a] Significantly different from corresponding enantiomer for the saline bolus group, $p < 0.05$.

[b] Significantly different from corresponding enantiomer for the cimetidine bolus group, $p < 0.05$.

[c] Significantly different from corresponding enantiomer for the saline infusion group, $p < 0.05$.

[d] Significantly different from corresponding enantiomer for the cimetidine infusion group, $p < 0.05$.

[*] Significantly different from corresponding enantiomer within same group, $p < 0.0125$.

Discussion

The aim of this study was to test the hypothesis that the renal elimination of sotalol enantiomers includes excretion *via* an organic cationic transport system in the proximal tubule. To test for the presence of an organic cationic transport mechanism for sotalol, cimetidine was co-administered, as it has been shown to be a relatively selective inhibitor of the proximal tubular secretion of organic cations [11], and appears to be devoid of non-specific effects on renal function [11]. Although sotalol enantiomers are zwitterions, in the blood greater than 90% of the total ionized molecule is in the cationic state at physiologic pH. Therefore, it is likely any tubular

secretion would be predominantly mediated by the cationic secretory mechanism. This study was conducted in rat model as rat has been shown to have similar sotalol enantiomer pharmacokinetics to humans [9]. In both human [7,8], and rat model [9], sotalol enantiomers are predominantly eliminated unchanged in urine with Cl_r values substantially greater than GFR, suggesting extensive tubular secretion. Cimetidine was given either as bolus or infusion, as the $t_{1/2}$ of cimetidine in rat is short (approximately 45 min [19]), and cimetidine interactions with the tubular secretion of concomitantly administered drugs has been reported to be concentration-dependent [11].

Cimetidine bolus resulted in a reduction in sotalol enantiomer Cl_s and Cl_r, by approximately 27 and 43%, respectively, compared with normal saline bolus controls. There were no significant differences between cimetidine bolus and saline controls in Cl_{nr} or Vd_{ss} of sotalol enantiomers. Interestingly, although cimetidine bolus significantly reduced the Cl_r of sotalol enantiomers, $t_{1/2\beta}$ and MRT values were not significantly different than for saline controls. A possible explanation for these findings is that the bolus dose of cimetidine resulted in a short-term reduction of sotalol enantiomer clearance, due to the short $t_{1/2}$ of cimetidine in rat.

Following cimetidine infusion, Cl_s, and Cl_r of sotalol enantiomers were reduced by approximately 45 and 59%, respectively, compared with saline infusion controls. Contrary to the results from the cimetidine bolus study, after cimetidine infusion, sotalol enantiomer $t_{1/2\beta}$ and MRT were significantly greater than saline infusion controls. Therefore, this result supports the notion that cimetidine produced a short-lived (concentration-dependent) reduction in the Cl_r of sotalol enantiomers. The concentration-dependent nature of interactions between cimetidine and the Cl_r of other drugs has previously been reported [23].

The reported values for Cl_r of sotalol enantiomers substantially exceed the literature value for GFR in rat (1.01 ml/min/100 g body weight [24]). In the present study, the ratio of Cl_r of sotalol enantiomers to the literature value for GFR was approximately 1.8 in saline controls. This ratio was reduced to approximately 1.0 and 0.8 following cimetidine bolus and cimetidine infusion, respectively. The ratio of 0.8

after cimetidine infusion may be due to a suppression in GFR due to the effects of anesthesia, and therefore the literature GFR is an overestimation in these rats. This ratio, however, also may suggest that passive or active tubular reabsorption is occurring which is not inhibited by cimetidine. Passive reabsorption of sotalol enantiomers is unlikely to be substantial, as the amine moiety in sotalol enantiomers would be nearly completely ionized in the renal tubules [14,15], and sotalol enantiomers have low lipophilicity, with an octanol:buffer partition coefficient of 0.039 [25,26].

The Cl_r/GFR ratio of 1.8 in controls suggests a net tubular secretion of sotalol enantiomers, and is likely an underestimate of net renal tubular secretion due to effects of anesthesia and sotalol protein binding. General anesthesia is expected to reduce cardiac output, renal plasma flow and GFR [27,28]: thus the literature value for GFR used in the calculation of the Cl_r/GFR ratios in this study is probably overestimated. The fraction of sotalol bound to plasma proteins also affects the estimation of net renal tubular secretion. The net renal tubular secretion clearance (Cl_{sec}) can be calculated as:

$$Cl_{sec} = Cl_r - GFR \cdot f_u$$

where f_u is the unbound fraction. Therefore, for given values of Cl_r and GFR, Cl_{sec} will increase with increasing values of f_u. Using an ultrafiltration technique, we have determined that the protein binding of sotalol enantiomers in serum from young and old humans and Sprague-Dawley rats is negligible (< 10%), and non-stereospecific [29]. Other reports of sotalol plasma protein binding in humans have ranged from 0% [26,30] to approximately 35% [7]. In any case, estimation of Cl_{sec} by comparing Cl_r with GFR without considering protein binding would underestimate Cl_{sec}, unless protein binding was negligible.

The observed substantial reductions in Cl_r in the presence of cimetidine is evidence that sotalol enantiomers are actively secreted by the kidney. Other β-blockers have been reported to be actively secreted by the kidney, including pindolol

[17,31] and pafenolol [32,33]. Although inhibition of active tubular secretion is likely the mechanism by which cimetidine reduces Cl_r of sotalol enantiomers, alternate explanations could include: cimetidine reduces Cl_r of sotalol enantiomers *via* non-specific effects on renal function, such as reduction of plasma flow or GFR; and/or cimetidine increases the plasma or tissue binding of sotalol enantiomers. Although cimetidine has been shown to reduce creatinine clearance, this is as a result of competitive inhibition of creatinine tubular secretion, and not as an effect on GFR, thus leading to underestimation of GFR [34]. Cimetidine does not appear to affect inulin clearance [35], blood urea nitrogen levels [36], or renal plasma flow [37]. Therefore, it is unlikely that cimetidine caused the observed substantial reduction in sotalol enantiomer Cl_r *via* non-specific alteration of renal function. It is also unlikely that cimetidine could cause a substantial decrease in sotalol enantiomer Cl_r by altering plasma or tissue binding. Both cimetidine [37] and sotalol [2,7,30] exhibit low plasma protein binding, therefore perturbations in plasma protein binding would not likely account for the observed magnitude of change in sotalol enantiomer disposition. Few studies have shown a significant effect of cimetidine on the volume of distribution or plasma protein binding of other basic drugs and, although in a few cases, reductions of these parameters have been demonstrated, the effect is likely clinically unimportant [37]. Cimetidine [38] and sotalol [39] enantiomers are extensively bound to peripheral tissues, which results in drug concentrations in some organs that are many times greater than those in plasma. Although cimetidine could competitively displace sotalol from either peripheral or plasma binding sites, such an interaction would likely increase Cl_r of sotalol enantiomers, rather than the observed reduction. Furthermore, such an interaction, if significant, should result in changes in Vd_{ss}, which was not observed. Therefore, it is not likely that the observed reductions in Cl_r were due to cimetidine-induced alterations in sotalol enantiomer distribution. The most likely mechanism by which cimetidine reduced sotalol enantiomer Cl_r, therefore, was *via* an inhibition of the active renal cation transport mechanism.

If, as it has been reported, the extraction of sotalol by the rat kidney approaches 1 [9], the clearance of sotalol would be dependent on renal blood flow

rather than intrinsic renal clearance. Therefore if cimetidine inhibited the active renal cation transport mechanism (decreasing the intrinsic clearance of sotalol by the kidney) it is unclear why renal clearance would be reduced by up to 60%, unless in unconscious rat model sotalol is moderately extracted by the kidney. In conscious rat, Cl_r values were reported to be approximately 35 ml/min/kg for each sotalol enantiomer after administration of the racemate. Renal blood flow in conscious rat can be estimated to be approximately 40 ml/min/kg [9], and thus the extraction ratio of sotalol by the kidney in conscious rat would be approximately 0.9. Therefore, in conscious rat it would be reasonable to expect that the renal clearance of sotalol enantiomers is predominantly determined by renal blood flow. In the current study with pentobarbital-anesthetized rats, renal clearance values for sotalol enantiomers (approximately 18 ml/min/kg) were substantially lower than that observed in conscious rat. Given that pentobarbital anesthesia reduces the cardiac output in rat by only approximately 20%, and recognizing the considerable homeostatic capacity of the kidney to maintain renal perfusion and GFR [28], the extraction ratio of sotalol by the kidney in pentobarbital-anesthetized rat may be as low as 0.45. Therefore, it is reasonable that in anesthetized rat the renal clearance of sotalol enantiomers is dependent both on renal blood flow as well as the intrinsic clearance of the kidney for sotalol. This rationale may explain why a substantial reduction in renal clearance of sotalol was observed with cimetidine co-administration in anesthetized rat, despite a likely negligible effect of cimetidine on renal blood flow. Furthermore, this rationale would predict that in conscious rat, where the extraction ratio of sotalol by the kidney is high, the interaction between cimetidine and sotalol may be attenuated, as in this case renal clearance becomes much less dependent on changes in the intrinsic clearance of the kidney. Furthermore, since in humans the extraction ratio of sotalol by the kidney is relatively low and renal clearance is thus affected by changes in intrinsic clearance, an interaction between cimetidine and sotalol enantiomers may be more pronounced.

As cimetidine could not affect the bioavailability of sotalol enantiomers in the present study, it remains to be explained why $Ae_{(0\text{-}6h)}\%$ was significantly reduced in

cimetidine-dosed groups compared with saline controls. The most likely explanation is that cimetidine reduced urinary excretion *and* urinary excretion of drug was incomplete after the 6 h collection. The $t_{1/2\beta}$ of sotalol enantiomers in control groups was approximately 1.5 h. Therefore, a 6 h urinary collection (4 half-lives) should capture approximately 95% of the total urinary excretion (ΣXu). In the cimetidine infusion group, however, sotalol enantiomer $t_{1/2\beta}$ was approximately 2.4 h, therefore only approximately 80% of ΣXu would be collected over the same sampling interval. Therefore, a smaller $Ae_{0\text{-}6h}$% would be expected for the cimetidine-dosed groups compared with controls, which was observed.

Since cimetidine inhibition of tubular secretion of drugs has been shown to be concentration-dependent [23], determination of the dosages of both cimetidine and sotalol enantiomers was an important consideration in study design. Based on literature values for cimetidine pharmacokinetics in rat [19], the 30 mg/kg bolus dose would result in an average plasma concentration (C_{av}) of approximately 1.5 μg/ml over the 6 h sample collection time period. In comparison, a C_{av} of approximately 0.83 μg/ml was observed in humans given 400 mg cimetidine twice daily [23]. In a previous study in rat model of cimetidine interaction in the pharmacokinetics of quinidine and lidocaine, a single intraperitoneal cimetidine dose of 60 mg/kg was given [40]. Interestingly, Cl_s and Cl_r of cimetidine in rat has been shown to be dose-dependent after intraperitoneal dosages of 10, 40, and 100 mg/kg [19], although differences in Cl_s and Cl_r between the 10 and 40 mg/kg groups did not appear to be significant. For rats given the cimetidine infusion (8.33 mg/h/kg), the resulting cimetidine steady-state concentrations would have been approximately 2.75 μg/ml.

A modest, but significant, stereoselectivity was observed in the disposition of sotalol in the cimetidine infusion group. In this group, Cl_s of R-sotalol was significantly greater than for S-sotalol, resulting in significantly larger AUC values (both total and partial) for S-sotalol. Stereoselectivity in Cl_r, however, was not observed. Stereoselectivity in renal elimination has been observed for sotalol [7], pindolol [17,31], quinidine and quinine [41], disopyramide [42], and verapamil [43]. The magnitude of the observed stereoselectivity in the present study was less than 5%,

and thus was likely of little consequence. There were no significant differences in S/R ratio between groups for any of the parameters reported, suggesting that cimetidine has no significant effect on sotalol enantiomeric ratio, and thus the cationic renal transport mechanism is not stereoselective for sotalol enantiomers. Therefore, the observed stereoselectivity is likely due to a small degree of stereoselectivity in tissue binding, Cl_{nr}, or a combination of these factors. In a report of steady-state sotalol enantiomer disposition in arrhythmia patients, a modest but significant stereoselectivity was observed in AUC (S > R), Cl_s, Cl_r, and Cl_{nr} (R > S) [7]. In a separate study, although similar trends in enantiomeric disposition were observed in younger healthy adults after single-dose administration, the stereoselectivity was not significant [8]. The comparability of the relative disposition of sotalol enantiomers observed in this paper to that reported in humans [7,8] supports rat as a useful model in pharmacokinetic studies of sotalol enantiomers.

In rat model, cimetidine significantly reduced the Cl_r and Cl_s of sotalol enantiomers. A similar sotalol-cimetidine interaction may be possible in humans, as an active renal excretory mechanism appears to play an important role in sotalol elimination in rat and human. To our knowledge, potential interactions between sotalol and cimetidine have not been reported. In fact, it has been suggested [44-48] that a clinically significant interaction between cimetidine and sotalol is unlikely, as sotalol undergoes little hepatic metabolism, and thus cimetidine-induced enzymatic inhibition effects on sotalol disposition would be inconsequential. Although this conclusion may be valid for metabolic reasons, it fails to consider that both drugs are substantially cationic at physiologic pH, are extensively eliminated actively from the kidney, and that cimetidine is a known competitive inhibitor of the renal organic cation transport mechanism. The Cl_r of pindolol enantiomers in human, for example, is reduced by approximately 30% with concurrent administration of 400 mg cimetidine twice daily [17]. The present study suggested that a significant drug-drug interaction exists between cimetidine and sotalol in rat model and could also exist in humans. Such an interaction resulting in elevated plasma concentrations of both sotalol enantiomers and cimetidine may have important clinical consequences.

In conclusion, it appears that rat is a good model for stereospecific studies of sotalol disposition. In this model, sotalol enantiomers were predominantly cleared *via* a renal cationic transport mechanism which could be inhibited by cimetidine co-administration. Although modest stereoselectivity in sotalol disposition was observed after cimetidine infusion in AUC (S > R) and Cl_s (R > S), the magnitude was not likely to have any clinical implications. As cimetidine had no effect on sotalol enantiomer concentration ratios, the cationic transport mechanism that mediates sotalol disposition was not likely stereoselective. Therefore, the small degree of stereoselectivity was likely caused by tissue binding and/or Cl_{nr}. Further research is necessary prior to extrapolating the results of this study to findings that may be possible when administering sotalol to humans.

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➢ CHAPTER 6 ≺

Determination of Protein Binding of Sotalol Enantiomers in Young and Elderly Adult Human and Rat Serum Utilizing an Ultrafiltration Technique♦

Introduction

There is a relative paucity of information regarding the protein binding of sotalol enantiomers in human serum or plasma. Although it has been previously reported that sotalol does not bind to human plasma proteins [1], a more recent study concluded that such binding was significant (38 and 35% for S- and R-sotalol, respectively) and stereoselective [2]. It is possible that the difference in the extent of protein binding between these two studies is due to a difference in the age and/or health of the subjects as the plasma samples analyzed in the former and latter studies were from healthy volunteers aged 24 to 53 y, and in patients having arrhythmias aged 43 to 74 y, respectively. Therefore, perhaps age and/or the presence of illness (e.g., arrhythmias) may significantly alter the protein binding of sotalol enantiomers. Such information would be useful in the interpretation of published reports of sotalol pharmacokinetics, as well as in the extrapolation of pharmacokinetic study results in young adults to the elderly. Furthermore, as rat has been shown to be a suitable model for sotalol enantiomer pharmacokinetic studies [3], it would be useful to determine if the protein binding of sotalol in young and elderly rats paralleled that in humans of comparable biological age.

In this report, the protein binding of sotalol enantiomers at physiological temperature and pH in serum from young and elderly adult humans and rats is presented.

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Materials and Methods

Specimens

Serum samples were obtained from healthy young male (32 ± 2 y, n = 5), and elderly (73 ± 6 y) male (n = 2) and female (n = 3) adult volunteers. Human blood samples were collected by direct venepuncture in 10 ml serum separator tubes (Corvac® Sherwood Medical, St. Louis, MO, U.S.A.), allowed to stand at room temperature for 1 h, then centrifuged at 1850 *g* for 20 min. The serum was separated and immediately frozen at -20° C. Three of the 10 human volunteers were taking normal adult doses of at least one drug at the time of the study (Table 6-1). Rat serum was also collected from young (8 weeks, n = 4) and elderly (60 weeks, n = 3) male Sprague-Dawley rats. Following catheterization of the right jugular vein under light ether anesthesia, rats were terminally bled *via* syringe. The blood was then immediately transferred to the serum separator tubes, and serum was collected as per human samples. The resulting serum was pooled for young and for old rats, and immediately frozen at -20° C.

Materials

Disposable ultrafiltration units (Microsep, Filtron Technology Corporation, Northborough, MA, U.S.A.) with a 3.5 ml sample cup and molecular weight cutoff of 30K were used for ultrafiltration. Racemic sotalol was kindly donated by Bristol-Myers Squibb (Ottawa, Ontario, Canada). All other chemicals and reagents were HPLC or analytical grade.

Ultrafiltration

Within 1 week after collection, frozen human serum samples and pooled rat serum samples were thawed at room temperature, and adjusted to pH 7.4 (Orion model 520A pH meter, Canadawide Scientific, Toronto, Ontario, Canada) with 0.05 *M* phosphate buffer, pH 5.0 (approximately 50 µl per ml of serum). Aliquots (3.5 ml) of serum were then spiked with sotalol to give enantiomeric concentrations of 250 ng/ml and 500 ng/ml, placed in the sample cups of the filter units and capped to

prevent evaporation and pH changes. The filtration units were then incubated in a 37° C temperature-controlled room for 30 min prior to centrifugation at 1850 *g* for 1.5 h utilizing a Dynac II centrifuge with a fixed-angle centrifugal rotor (Becton Dickinson, Parsipany, NJ, U.S.A.). A 300 µl aliquot of the resulting ultrafiltrate was removed for analysis of sotalol enantiomer content. A further 300 µl aliquot of each ultrafiltrate sample was used to ensure that protein concentrations in the ultrafiltrate were negligible, using a previously reported method [4]. Human serum samples for each volunteer were analyzed in duplicate at both spiked sotalol concentrations, while young and elderly pooled rat serum samples were analyzed in quadruplicate at each concentration.

Adsorption of Sotalol Enantiomers to the Ultrafiltration Device

To determine the extent of binding to the filter unit, the unit was filled with 0.01 *M* phosphate buffer (pH 7.4) containing sotalol enantiomers (250 or 500 ng/ml), and samples were withdrawn after 0.5, 1, and 2 h for determination of sotalol enantiomer concentration. To determine the extent of binding to the filter membrane, solutions of sotalol enantiomers (250 or 500 ng/ml) in 0.01 *M* phosphate buffer (pH 7.4) were analyzed for sotalol enantiomer concentration before and after ultrafiltration. These experiments were performed in duplicate at an ambient temperature of 37° C in a temperature-controlled room.

Evaporative Loss of Samples During Ultrafiltration

Evaporative loss of sample due to centrifugation was assessed by weighing each loaded filter unit before and after centrifugation. Each filter unit was also weighed prior to loading with sample, and the % evaporative loss was calculated as:

$$100 \bullet (W_B - W_A)/(W_B - W_D)$$

where W_D is the weight of the filter unit prior to loading with sample, and W_B and W_A are the weights of the loaded filter unit before and after centrifugation, respectively.

Quantification of Sotalol Enantiomers in Serum and Ultrafiltrate

Sotalol enantiomer concentrations in serum and ultrafiltrate were determined using normal-phase high-performance liquid chromatography with fluorescence detection [5]. Total (bound + unbound) sotalol enantiomer concentrations were determined in 300 µl aliquots of spiked serum samples prior to ultrafiltration. All four groups of serum samples (young human, elderly human, young rat, elderly rat) were analyzed in separate batches, utilizing a calibration curve and quality control samples prepared with blank pooled serum from the same group. Unbound sotalol enantiomer concentrations were determined in 300 µl aliquots of ultrafiltrate. As with serum samples, ultrafiltrate samples was analyzed in separate batches, utilizing a calibration curve and quality control samples prepared with corresponding blank ultrafiltrate from pooled serum from the same group. All calibration curves included five concentrations of sotalol enantiomers over the range of 83-1666 ng/ml. Calibration curves were linear ($r^2 > 0.999$). The mean error and coefficient of variation values for S-sotalol calibration curves were 6.3% and 6.5%, respectively, at 83 ng/ml, and 0.9% and 1.0%, respectively, at 1666 ng/ml. Corresponding values for R-sotalol calibration curves were comparable.

Determination of % Bound

Percentage of sotalol enantiomer bound to serum proteins was calculated as:

$$100 \bullet (C_T - C_F)/C_T$$

where C_T is the total (bound + unbound) sotalol enantiomer concentration in each serum sample before ultrafiltration, and C_F is the sotalol enantiomer concentration in the ultrafiltrate.

Statistical Analysis

Statistical analyses were performed using analysis of variance (ANOVA) with repeated measures, as both S- and R-sotalol concentrations were determined in each serum sample. A probability level < 0.05 was considered statistically significant.

Results and Discussion

Sotalol enantiomers were found to be negligibly (< 7%) and non-stereoselectively bound to young and old rat and human serum protein at physiological temperature and pH (Table 6-1). There were no significant differences in binding between young and old human and rat serum for either sotalol enantiomer, nor was binding concentration-dependent over the two sotalol concentrations studied.

As non-specific binding of drug to the ultrafiltration unit or membrane can result in overestimation of serum protein binding, the extent of such binding of sotalol enantiomers was determined in phosphate buffer at physiologic pH and temperature. Total sotalol enantiomer binding to both the filter unit and membrane was negligible (approximately 3%), and non-stereoselective (Table 6-2).

Although evaporative loss of samples during centrifugation could potentially result in concentration of ultrafiltrate and therefore underestimation of protein binding, evaporative loss of samples was negligible ($0.44 \pm 0.4\%$). Protein leakage through the membrane could also result in underestimation of protein binding, however, no detectable protein concentrations were found in any of the ultrafiltrate samples. The method used is capable of detecting leakage of $< 0.05\%$ of serum protein concentrations [4].

Table 6-1. Serum protein binding of sotalol enantiomers in young and elderly adult humans and rats (mean ± SD). Human serum samples were analyzed in duplicate, whereas pooled rat samples were analyzed in quadruplicate.

				Serum Protein Binding, %			
				250 ng/ml		*500 ng/ml*	
Subject	*Age*	*Concurrent Medications*	*Sex*	*S*	*R*	*S*	*R*
Young Humans		none					
1	29	tetracycline	male	6.7±1.9	6.7±1.9	0.3±0.5	0.3±0.5
2	32	none	male	4.0±1.9	5.3±3.8	5.7±1.4	5.3±0.9
3	31	none	male	7.3±2.8	7.3±2.8	3.7±3.3	4.7±2.8
4	31	none	male	2.0±2.8	0.0±0.0	3.7±2.4	3.7±1.4
5	35	none	male	1.3±0.0	2.0±0.9	5.0±2.4	5.0±2.4
	32±2			4.3±3.0	4.3±3.4	3.7±2.5	3.8±2.4
Elderly Humans							
1	65	none	male	0.0±0.0	0.0±0.0	10.7±0.0	10.3±0.5
2	81	none	female	3.3±0.9	3.3±0.9	8.0±9.4	9.3±9.0
3	72	verapamil	male	10.7±3.8	12.0±3.8	6.7±2.8	6.3±2.4
4	76	nifedipine, enalapril	female	7.3±4.7	6.7±3.8	4.3±2.4	4.0±2.8
5	70	none	female	1.3±3.8	0.7±0.9	2.3±3.3	2.7±2.8
	73±6			4.7±4.6	4.5±5.0	6.4±4.7	6.3±4.5
Young rats (pooled)	8 weeks		male	2.3±1.7	2.0±1.7	2.3±3.1	2.3±3.1
Elderly rats (pooled)	60 weeks		male	2.7±1.9	3.3±1.3	2.5±1.6	2.5±1.6

The negligible serum binding of sotalol reported in this study agrees with previous non-stereospecific reports in human [1] and dog [6]. A more recent report by Fiset *et al.* [2] found plasma protein binding of 38 and 35% for S- and R-sotalol, respectively; values which are greater than in the present study. A possible explanation for the greater magnitude of sotalol binding observed in the Fiset *et al.* [2] compared with the current study is that plasma samples in the Fiset *et al.* [2] study were from elderly patients being treated for arrhythmias, and thus it is possible that these patients may have increased plasma protein concentrations (e.g., α_1-acid glycoprotein, AAG) in comparison with the volunteers in the present study. As the binding of some drugs, including basic cardiovascular drugs such as propranolol and quinidine, is dependent on AAG concentration, it is conceivable that the binding of sotalol enantiomers could be relatively greater in arrhythmia patients than in healthy volunteers. Whether or not sotalol enantiomers bind to AAG, or if AAG

concentrations were in fact elevated in patients in the Fiset *et al.* [2] study is, however, unknown. It is also possible that methodological differences could account for the observed differences in sotalol enantiomer binding between the Fiset *et al.* [2] study (where blood collection tubes contained EDTA, and plasma binding was determined) and the present study (where no anticoagulant was used and serum binding was determined).

Table 6-2. Adsorption of sotalol enantiomers to filter membrane and filter unit (mean ± SD).

	% Bound to Filter Unit or Filter Membrane			
	250 ng/ml		*500 ng/ml*	
Time, h	*S*	*R*	*S*	*R*
Binding to filter unit, n = 2.				
0.5	0.0±0.0	0.0±0.0	0.2±0.9	0.2±0.9
1	1.3±1.9	1.3±1.9	0.7±1.9	0.7±1.9
2	0.7±2.8	0.7±2.8	0.3±0.5	0.3±0.5
Binding to filter membrane, n = 2.	2.0±2.8	2.0±2.8	1.7±2.4	2.3±3.3

The negligible binding of sotalol enantiomers observed in the current study would perhaps be expected based on a consideration of the limited lipid solubility of sotalol. A trend is seen with β-blockers whereby drugs with high lipid solubility, such as propranolol, are nearly completely bound to plasma proteins, whereas drugs with low lipid solubility, such as atenolol, are negligibly bound. The β-blockers with moderate lipid solubility, such as pindolol, are moderately bound to plasma proteins. Sotalol enantiomers have low lipid solubility, and thus would be expected to display minimal binding to plasma proteins. Lipophilicity has also been reported to play an important role in the stereoselectivity of binding, whereby the more lipophilic β-blockers are more likely to display stereoselective profiles in plasma and non-specific tissue binding [7]. A recent study [8] serves to illustrate the variability in the extent and stereoselectivity of binding of various β-blockers. In this study of binding to rat plasma containing high concentration of AAG, the mean enantiomeric binding percentage and S/R binding ratio were 68% and 1.4 for propranolol; 59% and 1.1 for oxprenolol; 34% and 2.6 for pindolol; and 0% for acebutolol [8].

A consequence of the insignificant serum binding of sotalol enantiomers is that concomitant treatment with agents that could potentially compete for protein binding would have little effect on sotalol enantiomer free fraction. Therefore, clinically significant drug-drug interactions with sotalol involving serum protein displacement would be unlikely. Also as a result of the negligible serum binding, total renal clearance (Cl_r) be directly compared with glomerular filtration rate (GFR) to determine if net renal tubular secretion (Cl_{sec}) is present, as [$Cl_{sec} = Cl_r - GFR \bullet f_u$] reduces to [$Cl_{sec} = Cl_r - GFR$] when the free fraction in serum (f_u) = 1. Using this approach with data from recent reports of sotalol enantiomer pharmacokinetics in healthy adult humans [9] and rat model [3], the renal clearance of both sotalol enantiomers exceeds estimated GFR by approximately 1.5 and three times, respectively. These results suggest that the renal clearance of sotalol enantiomers (which is their primary route of elimination in both species) involves a net secretion, likely involving the organic cationic renal transport system [10,11].

In conclusion, the binding of sotalol in human and rat serum at therapeutic concentrations and physiological temperature and pH was found to be negligible and non-stereoselective. It should be noted, however, that as only healthy subjects participated in the current study, it is possible that patients with disease or stress-induced increases in plasma protein concentrations could show substantially different magnitudes of plasma protein binding.

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➢ CHAPTER 7 ≺

Minor Routes of Elimination of Sotalol Enantiomers in Rat Model: Evidence of Intestinal Clearance♦

Introduction

The pharmacokinetics of sotalol enantiomers are characterized by nearly complete oral bioavailability, negligible plasma protein binding, significant tissue binding, and absence of biotransformation [1]. Following oral administration of the racemate to humans, the disposition of sotalol enantiomers shows minimal stereoselectivity [2,3]. Sotalol enantiomers are primarily eliminated as unchanged drug in the urine, *via* a combination of glomerular filtration and net tubular secretion [1]. Recovery of intact sotalol in the urine has been reported to be approximately 80% in humans following an oral dose [1]; approximately 93% in dog following an intravenous dose [4]; and approximately 84% in rat following an intravenous dose [5]. There is little information regarding the disposition of the remaining fraction of an administered dose in these species. In a non-stereospecific study where tritiated sotalol was administered intravenously to a dog model, approximately 93% of the dose was recovered in the urine, 3.4% in the feces, and only 0.7% in the bile. It is noteworthy that, although a minor route of elimination in dog, the amount of sotalol excreted in the feces was approximately 5-fold greater than the amount recovered in the bile, suggesting the possibility of intestinal clearance. Such intestinal clearance may be more significant in humans, where Bristol-Myers Squibb, in unpublished observations, found an average of 12.5% (range 3.6-26.8%) of an oral tritiated-sotalol dose was excreted in the feces [1].

In this report, the stereospecific biliary and intestinal clearances of sotalol enantiomers in rat model are presented, in order to estimate the extent and

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stereoselectivity of potential intestinal clearance. Rat has been reported to be a suitable animal model for pharmacokinetic studies on the disposition of sotalol enantiomers [5], and is convenient for determining the relative fraction of a dose eliminated in the bile and feces.

Materials and Methods

Chemicals

Racemic sotalol was a gift from Bristol-Myers Squibb (Ottawa, Ontario, Canada). Atenolol, the internal standard for the high-performance liquid chromatographic (HPLC) assay of sotalol, was obtained from ICI Pharma (Mississauga, Ontario, Canada). All other chemicals and reagents were HPLC or analytical grade.

Renal and Intestinal Clearances of Sotalol Enantiomers

Male Sprague-Dawley rats weighing approximately 325 g were used for the study. Following anesthesia *via* 50 mg/kg intraperitoneal sodium pentobarbital (M.T.C. Pharmaceuticals, Cambridge, Ontario, Canada), a total of 4 rats were catheterized with silastic tubing (0.025" i.d. X 0.047" o.d.; Dow Corning, Midland, MI, U.S.A.) at the right jugular vein. The animals were allowed to recover overnight prior to the experiment. During this time the animals were individually stored in 18" X 9.5" X 8" polycarbonate rodent cages, fasted, and given water *ad libitum*. During the experiment, rats were individually housed in metabolic cages. Racemic sotalol dissolved in normal (0.9%) saline was administered (5 mg/kg of each enantiomer) *via* the jugular vein catheter. The volume of the administered solution was 0.33 ml. Blood (0.25 ml) was collected from the jugular vein catheter immediately prior to, and at 5, 10, 20, and 30 min, then at 1, 2, 3, 4, 5, and 6 h after drug administration. Blood samples were immediately centrifuged and the plasma portion was separated and frozen at -20° C until analyzed. Between each blood sample collection 0.25 ml normal saline was administered *via* the jugular vein catheter as fluid replacement. Urine and

feces were collected quantitatively over intervals 0-48 and 48-60 h after drug administration. Urine and feces samples were kept frozen at -20° C until just prior to analysis.

Biliary Clearance of Sotalol Enantiomers

Male Sprague-Dawley rats weighing between approximately 390 and 430 g were used for the study. Prior to surgery and throughout the study, rats were anesthetized *via* intraperitoneal sodium pentobarbital (M.T.C. Pharmaceuticals, Cambridge, Ontario, Canada), dosed at 50 mg/kg initially, then 12.5 mg/kg as required to maintain anesthesia. A total of 4 rats were catheterized with silastic tubing (0.025" i.d. X 0.047" o.d.; Dow Corning, Midland, MI, U.S.A.) at the right jugular vein. A laparotomy was then performed, and the proximal portion of the common bile duct was catheterized with polyethylene tubing (Clay Adams, New Jersey, U.S.A.). Immediately after completion of the surgery, racemic sotalol dissolved in normal (0.9%) saline was administered (5 mg/kg of each enantiomer) *via* the jugular vein catheter. The volume of the administered solution was 0.39-0.43 ml. Blood (0.25 ml) was collected from the jugular vein catheter immediately prior to, and at 0.05, 0.1, 0.25, 0.5, 1, 2, 3, and 4 h after drug administration. Blood samples were immediately centrifuged and the plasma portion was separated and frozen at -20° C until analyzed. Between each blood sample collection 0.25 ml normal saline was administered *via* the jugular vein catheter as fluid replacement. Bile was quantitatively collected from 0-4 h post-dose. Also, small aliquots of bile (100 µl) were collected at time points 1, 2, and 3 h post-dose, for determination of biliary concentration of sotalol enantiomers. After collection, bile was immediately frozen at -20° C until analyzed.

Quantification of Sotalol Enantiomers in Plasma, Urine, Bile, and Feces

Sotalol enantiomer concentrations in the biological samples were determined using a previously reported stereospecific HPLC method [6], with the following modifications. Plasma samples (100-150 µl) were diluted with 300 µl of HPLC-grade water prior to analysis. Plasma calibration curve and quality control samples were

prepared using aliquots of 150 µl blank plasma, which were spiked with sotalol to give final enantiomeric concentrations over the range of 57-5714 ng/ml. Urine samples (aliquots of 25 µl) were analyzed after dilution with 400 µl HPLC-grade water. Urine calibration curve and quality control samples were prepared using aliquots of 25 µl blank urine, which were spiked with sotalol to give final enantiomeric concentrations over the range of 2-100 µg/ml. Bile samples (aliquots of 100 µl) were analyzed after dilution with 300 µl HPLC-grade water. Bile calibration curve and quality control samples were prepared using aliquots of 100 µl blank bile, which were spiked with sotalol to give final enantiomeric concentrations over the range of 100-5000 ng/ml. Fecal samples were weighed, manually ground with mortar and pestle to ensure a representative aliquot, then a 1.0 g aliquot was removed and homogenized with 9.0 ml HPLC-grade water. The homogenate was then centrifuged at 1850 *g* for 2 min, and an aliquot of 0.5 ml of the supernatant was analyzed for sotalol enantiomer content. Fecal calibration curve and quality control samples were prepared by spiking drug-free supernatant with sotalol to give enantiomeric concentrations over the range of 20-2000 ng/ml. Calibration curves used in the quantification of sotalol enantiomers in plasma, urine, bile and feces samples were linear ($r^2 > 0.999$). For all S-sotalol calibration curves generated in this study, the mean percent error [100•(actual-calculated)/actual] was 8.9% at the lowest calibration concentration, and 0.4% at the highest calibration concentration. Corresponding values for R-sotalol calibration curves were comparable.

Pharmacokinetic Data Analysis

The area under the plasma enantiomer concentration-time curve from time zero to infinity ($AUC_{0\text{-inf.}}$) and partial area from time zero to 4 h ($AUC_{0\text{-4h}}$) were calculated by the log trapezoidal rule, using a computer software program [7]. Systemic clearance (Cl_s) was calculated as $D/AUC_{0\text{-inf.}}$, where D was the enantiomeric dose administered. The renal clearance (Cl_r) of each enantiomer was estimated by dividing the 0-60 h cumulative urinary excretion of each sotalol enantiomer ($\Sigma X_{u(0\text{-}60h)}$) by the corresponding enantiomeric $AUC_{0\text{-inf.}}$ The biliary clearance (Cl_b) of each enantiomer

was estimated by dividing the 0-4 h cumulative biliary excretion of each sotalol enantiomer ($\Sigma X_{b(0\text{-}4h)}$) by the corresponding enantiomeric $AUC_{0\text{-}4h}$. The intestinal clearance (Cl_i) of each enantiomer was estimated by dividing the 0-60 h cumulative excretion of each sotalol enantiomer in the feces ($\Sigma X_{f(0\text{-}60h)}$) by the corresponding enantiomeric $AUC_{0\text{-}inf.}$ Mean plasma enantiomer concentration-time plots were generated for display purposes only by fitting the data to tri-exponential functions.

Statistical Analysis

Comparisons between the S- and R-sotalol pharmacokinetic parameters observed after administration of the racemate were assessed utilizing Student's *t* test for paired data. A probability level < 0.05 was considered statistically significant.

Results and Discussion

Renal and Intestinal Clearances of Sotalol Enantiomers

Following administration of racemic sotalol, the S- and R-enantiomer plasma concentration-time curves were virtually superimposable, and were well fitted to tri-exponential equations (Figure 7-1). A summary of pharmacokinetic parameters for the renal and intestinal clearances of sotalol enantiomers is presented in Table 7-1. The Cl_s of S- and R-sotalol were 28.8 and 31.0 ml/min/kg, respectively. Cl_r of S- and R-sotalol were 27.5 and 29.7 ml/min/kg, respectively, which accounted for approximately 95.5% of Cl_s. Cl_i of S- and R-sotalol were 1.21 and 1.30 ml/min/kg, respectively, accounting for approximately 4.2% of Cl_s. Total recovery of the administered dose as intact drug in the urine and feces was approximately 99.7 and 99.8% for S- and R-sotalol, respectively. This finding supports previous reports that sotalol is not metabolized [1,4]. No significant stereoselectivity was observed in the Cl_s, Cl_r, or Cl_i of sotalol.

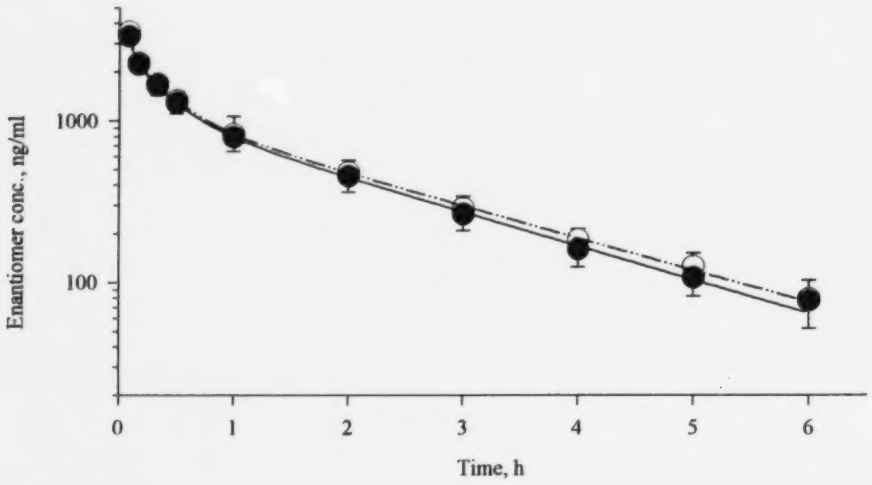

Figure 7-1. Mean plasma concentration versus time profiles for sotalol enantiomers after administration of the racemate. S-sotalol = open circles; R-sotalol = filled circles; dashed line = the tri-exponential function that best fits the data for S-sotalol; solid line = the tri-exponential function that best fits the data for R-sotalol; error bars represent standard error of the mean.

Biliary Clearance of Sotalol Enantiomers

After administration of racemic sotalol, the S- and R-enantiomer plasma concentration-time curves were virtually superimposable, and were well fitted to tri-exponential equations (Figure 7-2). A summary of the pharmacokinetic parameters for the Cl_b of sotalol enantiomers is presented in Table 7-2. Bile:plasma concentration ratios at 1, 2, and 3 h post-dose were approximately 1.4, 1.3, and 1.2, respectively, for both sotalol enantiomers (Figure 7-2). Despite sotalol enantiomer concentrations in bile that were comparable to simultaneous plasma sotalol concentrations, Cl_b values for S- and R-sotalol (0.0702 and 0.0689 ml/min/kg, respectively) accounted for only approximately 0.3% of Cl_s. Significant stereoselectivity (S- > R-sotalol) was observed in $AUC_{0\text{-}4h}$, $\Sigma X_{b(0\text{-}4h)}$, and Cl_b: the mean magnitudes of stereoselectivity were only 3.0, 4.6, and 1.9%, respectively, and thus likely of little consequence. An average bile flow rate of 16.3 ± 2.4 (SEM) µl/min was recorded during these experiments, which is in agreement with previous reports [8,9]. Cl_s values for sotalol enantiomers were

reduced by approximately 28% in the Cl_b study relative to the study to determine Cl_r and Cl_i. This is likely due to an effect of anesthesia, as rats were anesthetized in the Cl_b study, but were conscious for the Cl_r and Cl_i study. General anesthesia is expected to reduce cardiac output, renal plasma flow and GFR [10,11]. An anesthesia-induced reduction in Cl_s may have resulted in a value for Cl_b that is an underestimate in conscious rat. The magnitude of the potential underestimation in Cl_b resulting from a 28% reduction in Cl_s would not be expected to account for the observed substantial difference between Cl_b and Cl_i.

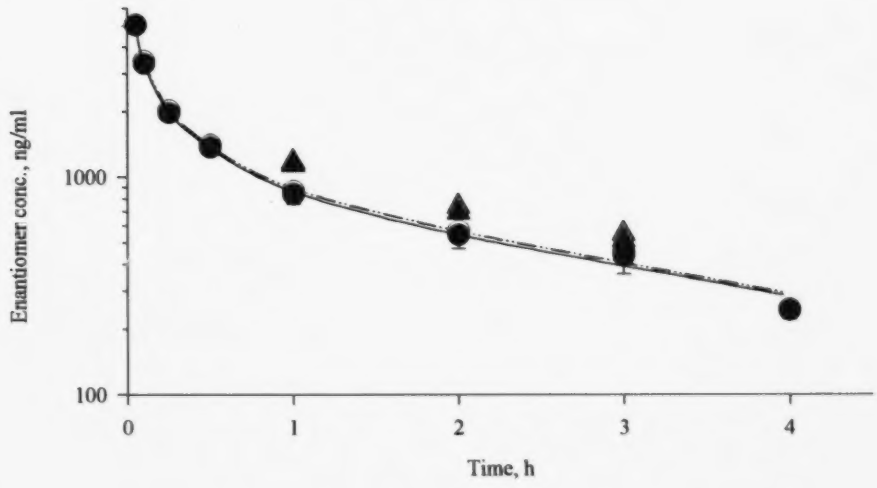

Figure 7-2. Mean plasma concentration versus time profiles for sotalol enantiomers after administration of the racemate; simultaneous concentrations of sotalol enantiomers in the bile. S-sotalol in plasma = open circles; R-sotalol in plasma = filled circles; S-sotalol in bile = open triangles; R-sotalol in bile = filled triangles; dashed line = the tri-exponential function that best fits the data for S-sotalol in plasma; solid line = the tri-exponential function that best fits the data for R-sotalol in plasma; error bars represent standard error of the mean.

In the current study, Cl_i was found to be approximately 18-fold greater than Cl_b. This finding is consistent with the notion that sotalol enantiomers undergo intestinal clearance. An alternative explanation is that sotalol enantiomers, if excreted in the bile as undetected metabolites (e.g., conjugates), could be converted back to

parent compound in the intestine where they would be detected in the feces as intact drug. This explanation, however, is unlikely, as there has been no reported evidence of sotalol metabolism. It is also possible that the recovery of sotalol enantiomers in the feces was due to cross-contamination of feces in the metabolic cages with sotalol in the urine. This is unlikely due to the efficient segregation of urine and feces due to the design of the metabolic cages, and the consistency of the results between rats. Therefore, given the insignificant excretion of sotalol in the bile, the most probable explanation for the presence of sotalol enantiomers in the feces is intestinal clearance.

In this study, it was found that intestinal clearance constituted approximately 4% of the total disposition of sotalol enantiomers. Interestingly, intestinal clearance has been reported for other β-blockers, including celiprolol [12], propranolol [12], pafenolol [8], and acebutolol [13]. In rat, after intravenous administration of pafenolol, 3% of the dose was eliminated as intact drug in the bile, whereas approximately 20% was eliminated by intestinal clearance. In humans, intestinal clearance may account for approximately 30% of pafenolol elimination following an intravenous dose [14]. The intestinal clearance of acebutolol in dog was found to be dependent on an active transport mechanism [13]. Notably, sotalol enantiomers are predominantly cleared from rat *via* an active renal cationic transport system [15,16]. It has been reported that the intestinal clearance of celiprolol is mediated by a saturable transport mechanism, which may be responsible for observed nonlinear absorption and bioavailability [12]. In rat, the intestinal clearance of celiprolol and propranolol were found throughout the entire intestine from pylorus to rectum, with no evidence of site specificity [12].

Table 7-1. Pharmacokinetic characteristics: Renal and intestinal clearances of sotalol enantiomers.

	Weight, g	*Dose,* μg	$AUC_{0\text{-}inf.}$, ng*h/ml		$Xu_{0\text{-}60h}$, μg		$Xf_{0\text{-}60h}$, μg		*Cls,* ml/min/kg		*Clr,* ml/min/kg		*Cli,* ml/min/kg	
			S	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*
Rat 1	325	1625	2708	2515	1529	1526	86.5	87.8	30.8	33.1	29.0	31.1	1.64	1.79
Rat 2	325	1625	2793	2540	1560	1563	63.3	63.7	29.8	32.8	28.6	31.6	1.16	1.29
Rat 3	325	1625	4582	4730	1553	1531	66.4	72.4	18.2	17.6	17.4	16.6	0.74	0.79
Rat 4	325	1625	2298	2061	1565	1591	58.7	53.5	36.3	40.4	34.9	39.6	1.31	1.33
Mean:	325	1625	3095	2962	1552	1553	68.7	69.4	28.8	31.0	27.5	29.7	1.21	1.30
SEM†*:*	0	0	507	600	8	15	6.1	7.3	3.8	4.8	3.7	4.8	0.19	0.21

Dose, enantiomeric dose; $AUC_{0\text{-}inf.}$, area under the plasma concentration-time curve from time zero to infinity; $Xu_{0\text{-}60h}$, cumulative urinary excretion from 0-60 h; $Xf_{0\text{-}60h}$, cumulative excretion in the feces from 0-60 h; Cls, systemic clearance; Clr, renal clearance; Cli, intestinal clearance.

† Standard error of the mean.

Table 7-2. Pharmacokinetic characteristics: Biliary clearance of sotalol enantiomers.

	Weight, g	*Dose,* μg	$AUC_{0\text{-}inf.}$, ng*h/ml		$AUC_{0\text{-}4h}$, ng*h/ml		$Xb_{0\text{-}4h}$, μg		*Cls,* ml/min/kg		*Clb,* ml/min/kg	
			S	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*
Rat 1	391	1955	5014	4816	3556	3458	7.58	7.23	16.6	17.3	0.0908	0.0891
Rat 2	430	2150	3025	3035	2384	2317	3.17	3.00	27.5	27.5	0.0515	0.0502
Rat 3	430	2150	4474	4190	3457	3318	5.20	4.94	18.6	19.9	0.0583	0.0576
Rat 4	425	2125	3953	3999	3210	3133	6.55	6.29	21.1	20.8	0.0800	0.0787
Mean:	419	2095	4117	4010	3152	3057	5.63‡	5.37	21.0	21.4	0.0702‡	0.0689
SEM†*:*	10	47	424	369	266	256	0.95	0.92	2.4	2.2	0.0092	0.0090

Dose, enantiomeric dose; $AUC_{0\text{-}inf.}$, area under the plasma concentration-time curve from time zero to infinity; $AUC_{0\text{-}4h}$, area under the plasma concentration-time curve from 0-4 h; $Xb_{0\text{-}4h}$, cumulative excretion in the bile from 0-4 h; Cls, systemic clearance; Clb, biliary clearance.

† Standard error of the mean.

‡ Significantly different from R-sotalol, $p < 0.05$.

In conclusion, following an intravenous dose of the racemate in rat model, sotalol enantiomers were primarily (96%) eliminated as unchanged drug in the urine. Although detectable concentrations of sotalol enantiomers were found in the bile, Cl_b was negligible. Cl_i was approximately 18-fold greater than Cl_b, and represented approximately 4% of Cl_u. This finding suggests the presence of intestinal clearance of sotalol enantiomers. Although the extent of intestinal clearance in rat model was minimal, this route of elimination may, perhaps, be more prominent in humans. Furthermore, it is possible that intestinal clearance assumes more importance in situations where elimination *via* the kidneys is compromised (e.g., in the debilitated elderly).

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General Discussion and Conclusions

In this study, the pharmacokinetics of sotalol enantiomers were investigated. Following oral administration of racemic sotalol to volunteers, the disposition of sotalol enantiomers was found to be non-stereoselective. This was a surprising finding, considering that the currently known disposition of most other β-blockers shows significant stereoselectivity. Sotalol enantiomers were found to be predominantly eliminated as intact drug in the urine. Consequently, renal clearance accounted for approximately 75% of oral clearance. The disposition of the remaining fraction of the dose remained unaccounted for. The mean renal clearance of each sotalol enantiomer was approximately 150 ml/min., which was greater than the mean estimated glomerular filtration rate of 105 ml/min., suggesting the presence of net active renal tubular secretion.

Despite the similar time-courses of sotalol enantiomers after racemate administration, it was hypothesized that an enantiomer-enantiomer interaction may yet exist. This hypothesis was considered plausible from both pharmacokinetic and pharmacodynamic perspectives. Pharmacokinetic enantiomer-enantiomer interactions have been reported for drugs including ibuprofen [1,2], disopyramide [3], and terbutaline [4]. A pharmacodynamic interaction may result as a consequence of the differing pharmacology of the enantiomers. Given the greater β-blocking potency of R-sotalol compared with S-sotalol, physiological changes due to the presence of β-blockade could simultaneously affect the disposition of both enantiomers after racemate administration. However, if pure enantiomers were administered, the presence (administration of pure R-sotalol) or absence (administration of pure S-sotalol) of β-blockade could effect differences in the disposition of the enantiomers. This consideration assumes added importance as the pure enantiomer S-sotalol is currently undergoing clinical trials as an antiarrhythmic.

To investigate the possibility of an enantiomer-enantiomer interaction, it was undertaken to determine sotalol enantiomer disposition after administration of racemate and pure enantiomer. As administration of the pure R- and S-sotalol

enantiomers in humans had not yet been approved, the Sprague-Dawley rat was chosen as a model. The model was deemed suitable as, in man, the disposition of sotalol enantiomers following racemate administration was not stereoselective and the drug was excreted mainly intact in the urine. It was found that the administration of pure S-sotalol resulted in significantly reduced systemic and renal clearance values compared to those observed after administration of the racemate. The most likely explanation for this finding is that when the β-blocker R-sotalol is administered (either as pure enantiomer or as the racemate) renal blood flow is increased, which results in greater renal clearance of sotalol than when the S-enantiomer is given alone.

The notion that the enantiomer-enantiomer interaction is related to a perturbation in renal flow is supported by the observation that in rat model sotalol enantiomers are highly extracted by the kidney (clearance approaches renal blood flow). Therefore, sotalol enantiomer clearance in rat is dependent upon renal blood flow. This finding is in marked contrast to humans, where the renal clearance of sotalol enantiomers is much less than renal blood flow. Therefore, in humans, the renal clearance of sotalol is dependent upon the intrinsic clearance of the kidney and the fraction of sotalol unbound to plasma proteins, and is not dependent upon renal blood flow. Thus even if the renal blood flow in humans was relatively greater after administration of the racemate compared with S-sotalol administered alone, it is likely that the disposition of sotalol would be negligibly affected.

It was observed that in both humans and in rat model the renal clearance values for sotalol enantiomers substantially exceeded the glomerular filtration rate (GFR). The hypothesis that sotalol enantiomers were actively secreted by the cationic renal transport mechanism was confirmed in rat model by co-administration of cimetidine, a known inhibitor of renal tubular secretion of organic cations. Continuous cimetidine infusion resulted in a reduction of the sotalol renal clearance by approximately 60%, and equal to the GFR in rats. As the presence of cimetidine had no effect on the enantiomeric ratio (approximately unity), the cationic renal transport mechanism is not stereoselective for sotalol enantiomers. Based on these findings, it is likely that renal tubular secretion accounts for approximately 30% and 60% of the disposition of

sotalol enantiomers in humans and rats, respectively. As these results reflect studies done with healthy young adult subjects, corresponding values for patients may be considerably different.

In the estimation of renal tubular secretion values, the plasma protein binding of sotalol enantiomers was assumed to be negligible, based on non-stereospecific reports in the literature. A study by Fiset *et al.* [5] in 1993, however, concluded that sotalol binding to plasma proteins was significant and stereoselective. As the subjects in the Fiset *et al.* study [5] were elderly patients with ventricular arrhythmias, it was hypothesized that age and/or the presence of illness (e.g., arrhythmias) may significantly alter the protein binding of sotalol enantiomers. Such information would be useful in the interpretation of published reports of sotalol pharmacokinetics, in the extrapolation of pharmacokinetic study results in young adults to the elderly, and in the accurate estimation of renal tubular secretion in various patient groups. Furthermore, as rat had been used as a model for sotalol enantiomer pharmacokinetic studies, it was of interest to determine if the protein binding of sotalol in young and elderly rats paralleled that in humans of comparable biological age. It was found that the plasma protein binding of sotalol in young and elderly adult human and rat serum at therapeutic concentrations and physiological temperature and pH was negligible and non-stereoselective. Although the discrepancy between this finding and that reported by Fiset *et al.* [5] may be attributed to differences in composition of the plasma from the two groups of elderly subjects (e.g., concentration of α_1-acid glycoprotein), it is perhaps more likely due to experimental differences. While both studies utilized ultrafiltration techniques, the methods and conditions utilized in the protein binding determinations were not described by Fiset *et al.* [5]. Therefore, differences in experimental design between the two studies (e.g., pH, temperature, drug concentrations) may be responsible for the differences in the observed magnitudes of sotalol enantiomer protein binding.

Finally, although sotalol enantiomers are primarily eliminated as unchanged drug in the urine, there is little information regarding the disposition of the remaining fraction of an administered dose. As sotalol is not metabolized, it was hypothesized

that sotalol enantiomers may be cleared by the intestine. Intestinal clearance has been shown for other β-blockers, including celiprolol [6], propranolol [6], pafenolol [7], and acebutolol [8]. In the case of pafenolol, intestinal clearance accounts for approximately 30% of the elimination of the drug following an intravenous dose. It was undertaken to determine the biliary and intestinal clearance of sotalol enantiomers in rat model. By administering the sotalol intravenously, the possibility of incomplete gastrointestinal absorption was avoided. It was found that although sotalol was present in the bile in concentrations similar to plasma levels, the contribution of biliary clearance to systemic clearance was negligible. Intestinal clearance was found to be approximately 18-fold greater than biliary clearance, and represented approximately 4% of systemic clearance. The administered dose was completely recovered as intact drug in the urine and feces.

In summary, the new findings reported as a result of this study include: 1) sotalol disposition in humans and rat model following administration of the racemate is non-stereoselective; 2) in rat, the systemic and renal clearances of S-sotalol are significantly reduced when administered as the pure enantiomer compared with the racemate, which may be explained by the presence of a pharmacodynamic enantiomer-enantiomer interaction (i.e., an increase in renal blood flow by the β-blocker R-sotalol); 3) the pharmacodynamic enantiomer-enantiomer interaction observed in rat would likely not be observed in humans, where the renal clearance of sotalol enantiomers is independent of renal blood flow; 4) the renal elimination of sotalol enantiomers includes both glomerular filtration and active cationic tubular transport mechanisms; 5) the serum binding of sotalol enantiomers is negligible; 6) sotalol enantiomers are excreted intact in the bile, and to a much larger extent in the feces, suggesting the presence of intestinal clearance; and 7) after administration of the racemate, systemic, renal, biliary, and intestinal clearances are non-stereoselective.

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References

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